J|A|C|S
COMMUNICATIONS

Published on Web 04/17/2004

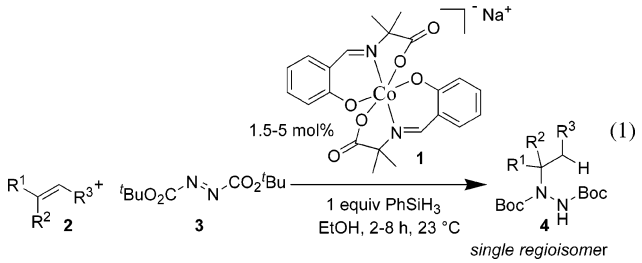
Convenient Synthesis of Alkylhydrazides by the Cobalt-Catalyzed Hydrohydrazination Reaction of Olefins and Azodicarboxylates

Jérôme Waser and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Hönggerberg, CH-8093 Zürich, Switzerland

Received March 7, 2004; E-mail: carreira@org.chem.ethz.ch

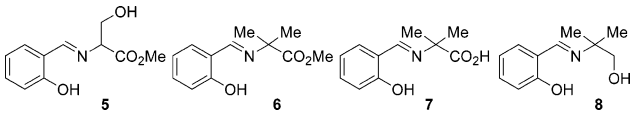
Amines and related functional groups are critical subunits in a wide range of pharmaceutical substances and other biologically active agents.[1] Therefore, the development of new methods for their synthesis is important, particularly when they allow access to a large range of functionalized amines starting from simple, commercially available compounds. Alkyl hydrazines can serve as useful precursors to amines and can also be employed in numerous ways for the assembly of synthetic building blocks.[1,2a] The preparation of *N*-alkyl substituted hydrazines is generally effected through the displacement reaction of alkyl halides and hydrazines,[2a] nucleophilic additions to hydrazones[2b] or azodicarboxylates,[2c−g] conjugate additions of hydrazines to Michael acceptors, or the ene reaction of olefins and reactive azodicarboxylates.[2h,i] However, the synthesis of *N*-alkyl hydrazides by direct C═C functionalization of unactivated olefins is unprecedented. Herein, we report such a process, wherein treatment of an olefin **2** with di-*tert*-butyl azodicarboxylate (**3**), $PhSiH_3$, and the simple Co(III) catalyst **1** in ethanol at 23 °C affords the Markovnikov hydrazide product **4** for a broad range of olefins in 62−94% yield (eq 1).



(1)

The use of simple cobalt complexes and silanes for the oxyfunctionalization of olefins has been pioneered by Mukaiyama and Isayama.[3] Thus, the generation of alcohols directly from olefins is accomplished upon their treatment with a mixture of oxygen and silanes in the presence of complexes such as $Co(acac)_2$, $Co(modp)_2$, or $Co(dpm)_2$.[3,4] It is interesting to note that in these processes the overall hydration of an olefin, itself an isohypsic reaction, is effected under conditions that include both oxidants (O_2) and reductants (silanes). Thus, the successful development of the reaction process necessarily demanded the careful screening and optimization of catalysts, solvents, and reaction conditions to ultimately furnish a finely tuned reaction system that avoids overoxidation of the first-formed peroxides to ketones and other problematic side reactions. Although the mechanistic details of these processes remain unclear, it has been suggested that the combination of the silane and the cobalt complex leads to the formation of a cobalt hydride that subsequently participates in olefin hydrocobaltation.[3c] The organocobalt intermediate so produced then adds to oxygen. In considering this mechanistic hypothesis, we sought to investigate whether a related process would be feasible with an N═N acceptor. Specifically, the use of an azodicarboxylate as a substitute for oxygen would lead to an olefin hydrohydrazination reaction.

Chart 1



At the outset of our investigations, we failed to observe any olefin hydrohydrazination reaction with the complexes and conditions that had proven successful in the olefin oxygenation reactions, $Co(acac)_2$, $Co(modp)_2$, or $Co(dpm)_2$,[3,4] or simple commercially available cobalt salts, $Co(OAc)_2$, $CoCl_2 \cdot 6H_2O$, or $Co(NO_3) \cdot 6H_2O$, and $PhSiH_3$ or Et_3SiH along with DEAD in ethanol, THF, or 1,2-dichloroethane at 23 °C. In general, we only observed direct reduction of DEAD to the corresponding hydrazine dicarboxylate. Because a number of reactive agents could be generated in the course of the reaction, including species such as alkylcobalts (R−Co), hydridocobalts (Co−H), (alkyl)hydridocobalts (R−Co−H), or silylhydridocobalts ($R(H_{3-x}Si)Co-H$),[5] the successful implementation of an olefin hydrohydrazination reaction would necessitate careful balancing of the reactivity of the various cobalt intermediates, which would be in competition for the electrophilic azodicarboxylate.

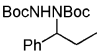
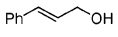
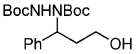
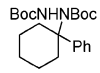
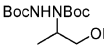
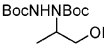
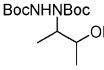
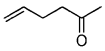
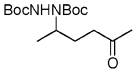
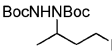
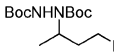
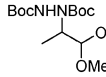
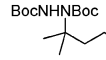
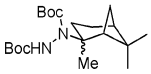
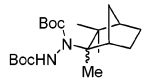
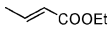
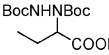
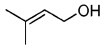
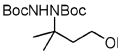
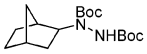
Remaining with our analogy between O_2 and azodicarboxylates, we expanded our study to include various coordination complexes of cobalt known to mediate epoxidation or peroxidation reactions of alkenes or alkanes.[6] Cobalt complexes were prepared from Schiff base ligands **5**−**8**, among others (Chart 1). The complexes derived from **5** and **6** were prepared by mixing the respective ligand and $CoCl_2$ in CH_3CN, giving the green Co(II)-complexes.[6] The complexes incorporating **7** and **8** were synthesized from $Co(NO_3) \cdot 6H_2O$, salicylaldehyde, amines, NaOH, and H_2O_2 in ethanol, furnishing the red Co(III)-complexes.[7]

The reaction of 4-phenyl butene with 1.0 equiv of $PhSiH_3$ and 1.5 equiv of DEAD or the more hindered di-*tert*-butyl azodicarboxylate (**3**) with 1−10 mol % of Co-complex was used as a test case. We were pleased to discover that in ethanol catalyst **1** (derived from **7**) proved to be most promising, giving the Markovnikov product exclusively in 35% yield using DEAD and in 85% yield using di-*tert*-butyl azodicarboxylate (**3**).

Under the optimized conditions, the hydrohydrazination of a wide range of cyclic and acyclic olefins (monosubstituted, 1,1- and 1,2-disubstituted, trisubstituted) is observed using 1−5 mol % of Co-complex **1** at 23 °C over 2−8 h in useful yields (Table 1). Monosubstituted, 1,1-disubstituted, and trisubstituted olefins give exclusively the Markovnikov product. For 1,2-disubstituted olefins, the selectivity is governed by electronic effects. Thus, phenyl substitution (entries 1−6) leads to formation of the benzylic hydrazide, while the presence of an ester (entry 18) leads to the C_α hydrazide ester. It is interesting to note that the reaction is highly tolerant of other functionalities; in particular, the hydrohydrazination leaves untouched primary bromides (entry 11) and ketones (entry 10). The only limitations observed to date involve unactivated 1,2-disubstituted olefins such as crotyl alcohol and cyclohexene which

10.1021/ja048698u CCC: $27.50

Table 1. Hydrohydrazination Reaction of Olefins (Eq 1)

Entry	Alkene	Product	Yield[a]
1			86%[b]
2			88%[b]
3			88%
4			91%
5			94%
6			80%[c]
7			78%
8			76%
9			73% (d.r. 1:1)
10			76%
11			90%
12			85%
13			70%
14			88%[c]
15			84% dr 2:1-3:1
16			69% dr>5:1
17			90%
18			66%[c]
19			70%
20			66%
21			62%[c]
22			74%[c]

[a] Standard conditions: 0.5 mmol of alkene, 0.5 mmol of $PhSiH_3$, 0.75 mmol of **3**, 5 mol % of catalyst **1**, 2.5 mL of ethanol at 23 °C under N_2. [b] 0.5 mmol of alkene was added as a solution in 1 mL of CH_2Cl_2 using 1.5 mol % of catalyst **1**. [c] 0.5 mmol of alkene, 0.75 mmol of $PhSiH_3$, and 1.0 mmol of **3** were used.

afford adducts in 40% and 25% yields, respectively. Cyclooctene and cyclopentene (entries 21 and 22), however, are good substrates for the reaction.

Due to the obvious complexity of the mechanism, any model can only be highly speculative at the current level of development.

Scheme 1

As shown in Scheme 1, we hypothesize that a hydridocobalt intermediate **9** is generated which undergoes chemoselective addition to the olefin **2** in preference to **3** to afford an organocobalt species **10**.[8] Intermediate **10** then adds to the N═N electrophile to give a cobalt hydrazide **12**. Subsequent reaction of **12** with the silane through a σ-bond metathesis process[9] furnishes the hydrohydrazination product **13** and regenerates the hydridocobalt **9** necessary for catalytic turnover.

In conclusion, we report a novel olefin hydrohydrazination reaction that affords alkyl hydrazides for a broad range of olefins. The salient features of this unprecedented process include the ease of execution (unpurified alcoholic solvents, room temperature), the availability of the reaction components ($PhSiH_3$, **3**, olefins), and the range of products accessible. Further studies are being conducted to understand the fundamental aspects of the process and develop even more efficient catalytic systems.

Acknowledgment. We are grateful for the support of this research by Sumika Ltd., Japan.

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

References

(1) Brown, B. R. *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Oxford University: New York, 1994.
(2) (a) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Ricci, A. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000. (d) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395. (e) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397. (f) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (g) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (h) Brimble, M. A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5261. (i) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999.
(3) (a) Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 179. (b) Isayama, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305. (c) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595. (d) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *6*, 1071. (e) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, *4*, 573.
(4) modp = 1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato; dpm = dipivaloylmethanato.
(5) Tada, M. *Rev. Heteroat. Chem.* **1999**, *20*, 97.
(6) Punnyamurthy, T.; Bhatia, B.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *Tetrahedron* **1997**, *53*, 7649.
(7) Burrows, R. C.; Bailar, J. C. *J. Am. Chem. Soc.* **1966**, *88*, 4150.
(8) The regioselectivity of the hydrocobaltation step has been studied, see, for example: Derenne, S.; Gaudemer, A.; Johnson, M. D. *J. Organomet. Chem.* **1987**, *322*, 229. The chief differences observed between the various Co-complexes prepared from **5**−**8** arise from the competitive reduction of the azodicarboxylate versus hydrocobaltation. We hypothesize that the steric bulk associated with di-*tert*-butyl azodicarboxylate (**3**) is critical in minimizing its reduction. The effect of the ligands in this respect is not clear and is the subject of ongoing investigations.
(9) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103.

JA048698U