J|A|C|S COMMUNICATIONS

Published on Web 08/28/2009

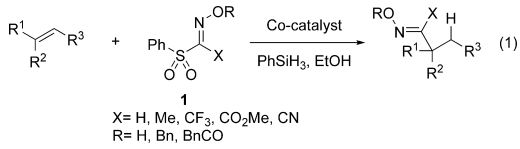
Cobalt Catalyzed Functionalization of Unactivated Alkenes: Regioselective Reductive C−C Bond Forming Reactions

Boris Gaspar and Erick M. Carreira*

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

Received June 14, 2009; E-mail: carreira@org.chem.ethz.ch

The chemistry of oximes and oxime ethers is rich and well described in the literature.[1] They can be transformed into carbonyl and nitro compounds, amines, hydroxylamines, or nitriles rather easily. Oximes are also present in a number of compounds with a wide spectrum of biological activities.[2] Although many methods for the synthesis of oximes have been developed, none involves direct synthesis from unactivated alkenes. The ability to prepare oximes from olefins would not only expand the range of functionalization reactions of alkenes but also open up new strategic approaches in the synthesis of complex molecules.[3,4] Herein, we report a novel olefin functionalization reaction which homologates olefins to afford aldoximes (X = H) and oximonitriles (X = CN) (eq 1). The transformation is enabled by carrying out in tandem an olefin hydrocobaltation reaction followed by reaction of the organocobalt species with sulfonyl oximes **1**.

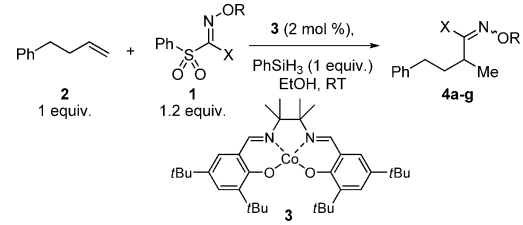


(1)

We have documented a mild Co-catalyzed hydrocyanation of olefins with *p*-toluenesulfonyl cyanide and phenylsilane that operates under mild conditions and avoids handling of HCN at elevated pressures and temperatures.[5,6] We have been interested in expanding the nature of reagents that can intercept the organocobalt intermediate, leading to the formation of new C−C bonds. In this respect, we sought alternatives to the more common transformations involving olefin hydrocyanation, -formylation, and -carboxylation reactions. Thus, we have examined various sulfonyl oxime ethers **1a**−**g** and their utility and compatibility with the hydrocobaltation reaction. We speculated that these could display reactivity similar to that observed with tosyl cyanide, by undergoing nucleophilic attack at C (and not S) and subsequently ejecting the *p*-toluenesulfonyl group. A selection of phenyl sulfonyl oximes **1a**−**d** have been shown to participate in reactions with radicals generated from alkyl iodides, alkyl allyl sulfones, or alkyl phenyl tellurides.[7] Yet, their reaction with olefins and in the presence of organometallic reagents is unprecedented. Thus at the outset of our investigations it was unclear whether the putative organocobalt intermediates generated would be compatible with reagents **1** or the end products present in the reaction mixture.

We commenced our studies by mixing 4-phenylbutene (**2**) with various phenyl sulfonyl oximes **1** in the presence of Co catalyst **3** and phenylsilane in ethanol at RT (Table 1). We were pleased to observe that phenylsulfonylmethanal *O*-benzyloxime (**1a**) (entry 1) undergoes reaction with **2** to provide product **4a** in 99% yield. The methyl and trifluoromethyl ketoximes **1b** and **1c** respectively (entries 2 and 3) failed to participate in any reaction; we suspect that this is most likely a consequence of steric congestion. Accordingly, changing to a somewhat smaller ethylester group was beneficial, and reagent **1d** (entry 4) gave product **4d** in 61% yield. Replacing the *O*-benzyl group with a phenylacetyl protecting group had a detrimental effect on the reaction as reagent **1e** (entry 5) furnished **4e** in merely 37% yield and free oxime **1f** (entry 6) did not participate in the reaction at all. We have also prepared *N*-(benzyloxy)-1-(phenylsulfonyl)-methanimidoyl cyanide **1g** (entry 7)[8] and examined it in the reaction, where it proved to efficiently afford the corresponding oximonitrile **4g** in 95% yield. This represents a convenient one-step preparation of this class of compounds that have otherwise been assembled through multistep sequences.[9] Interestingly, reagent **1g** is bench stable and easy to prepare, yet, to the best of our knowledge, it has not been examined in radical transfer processes.[7]

Table 1. Examination of Various Phenyl Sulfonyl Oximes **1** in the Cobalt Catalyzed Functionalization of 4-Phenylbutene (**2**)



entry	reagent	time[a] [h]	yield [%]
1	**1a** (R = Bn, X = H)	3	99
2	**1b** (R = Bn, X = Me)	3	0
3	**1c** (R = Bn, X = CF_3)	3	0
4	**1d** (R = Bn, X = CO_2Et)	2.5	61
5	**1e** (R = BnCO, X = CO_2Me)	2	37
6	**1f** (R = H, X = CO_2Me)	3	0
7	**1g** (R = Bn, X = CN)	2	95

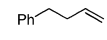
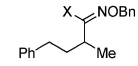
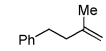
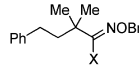
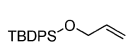
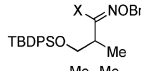
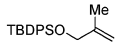
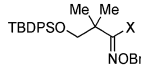
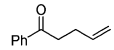
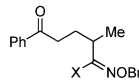
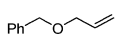
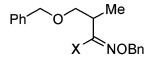
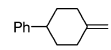
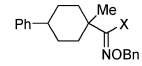
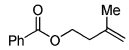
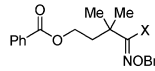
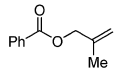
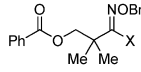
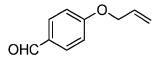
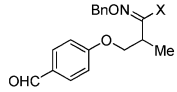
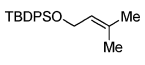
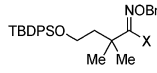
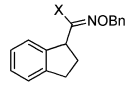
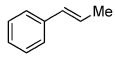
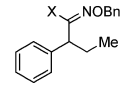
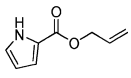
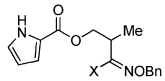
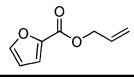
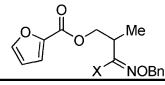
[a] The reaction time refers to complete consumption of the alkene. In cases where no desired product was observed, the starting olefin underwent reduction and/or double bond migration to form the internal alkene.

The scope of the new C−C forming reactions with the two most efficient reagents **1a** and **1g** was examined next (Table 2). The reaction displays excellent Markovnikov selectivity with both reagents, as only the branched products were detected. This is most likely the consequence of regioselective hydrocobaltation of the double bond, positioning cobalt on the more substituted carbon.[10] Simple alkenes (entries 1 and 2), protected alcohols (entries 3, 4, and 6), esters (entries 8 and 9), and ketones (entry 5) are well tolerated, and both sulfonyl oximes **1a** and **1g** give comparable high yields. However, the conversion of the more challenging trisubstituted alkenes (entry 11) or styrene derivatives (entries 12 and 13) with sulphonyl oxime **1a** was very low. Yet, the same substrates undergo functionalization by **1g** cleanly. Thus the corresponding products can be isolated in good yields with the styrene derivatives (entries 12 and 13) with complete selectivity for the formation of a benzylic C−C bond.

Reagent **1g** also proved superior in the case of substrates with sensitive functional groups such as an aldehyde (entry 10), which remained untouched under the reductive conditions, selectively providing the desired product in 86% yield. Even pyrrole and furan derived heterocycles (entries 14 and 15) were tolerated in the process giving the corresponding products in good yields. However, α,β-unsaturated esters such as ethyl crotonate failed to provide the desired aldoxime or oximonitrile compounds.

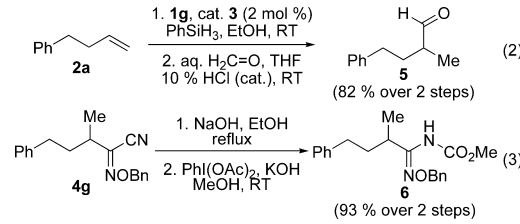
10.1021/ja904856k CCC: $40.75

Table 2. Scope of the Cobalt Catalyzed Functionalization of Alkenes[a]

	Alkene	Product	Yield [%] X= H	Yield [%] X= CN
1			99	95
2			71	91
3			90	87
4			82	80
5			63	82
6			64	83
7			33	80
8			79	-
9			-	82
10			-	86
11			-	84
12			-	88
13			-	65
14			-	90
15			-	74

[a] General procedure: catalyst **3** (2 mol %), alkene (0.5 mmol), reagent **1a** or **1g** (0.6 mmol), EtOH (2 mL), CH_3CN (0.5 mL), $PhSiH_3$ (0.5 mmol), argon, 23 °C.

Next, we examined the possibility of elaborating the products formed in the Co-catalyzed process to other useful compounds. From the numerous options we had in the case of oxime ethers, we decided to transform them into the corresponding aldehyde, as this would constitute hydroformylation of the starting olefin. As expected, we were able to convert our test alkene **2a** directly into aldehyde **5** in a two-step procedure (eq 2). After hydrooximation the corresponding product **4a** was hydrolyzed with formaldehyde in the presence of catalytic amounts of HCl to afford exclusively the branched aldehyde **5** in 82% yield. This protocol thus provides an alternative to a hydroformylation sequence. The oximonitrile functional group in **4g** could be transformed into an amidoxime, a group which is present in many biologically active compounds[11] such as fungicides[11b] or insecticides.[11c] Indeed, a two-step sequence (eq 3) starting with the hydrolysis of **4g** to the corresponding amide followed by Hofmann rearrangement using $PhI(OAc)_2$[12] afforded *N*-carbalkoxy-*O*-benzyl amidoxime **6** in 93% yield.



In summary, we have documented a new cobalt-catalyzed C−C bond forming reaction, which introduces an *O*-benzyloxime or oximonitrile onto unactivated double bonds. The reaction is tolerant to a range of functional groups and displays complete Markovnikov selectivity. The reaction conditions are mild (EtOH, ambient temperatures), and the products can be further transformed into aldehydes as well as amidoximes. Future work will be dedicated to study the potential applications of these processes in the synthesis in more complex settings as well as the development of asymmetric versions.

Acknowledgment. We thank the Swiss National Foundation for support of this research (Grant 2-00020-119838).

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) (a) Mikhaleva, A. I.; Zaitsev, A. B.; Trofimov, B. A. *Russ. Chem. Rev.* **2006**, *75*, 797–823. (b) Abele, E.; Lukevics, E. *Org. Prep. Proced. Int.* **2000**, *32*, 235–264. (c) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 125–139. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. (e) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946.
(2) (a) Abele, E.; Abele, R.; Rubina, K.; Lukevics, E. *Chem. Heterocycl. Compd.* **2005**, *41*, 137–162. (b) Abele, E.; Abele, R.; Lukevics, E. *Chem. Heterocycl. Compd.* **2004**, *40*, 1–15. (c) Abele, E.; Abele, R.; Dzenitis, O.; Lukevics, E. *Chem. Heterocycl. Compd.* **2003**, *39*, 3–35. (d) Abele, E.; Lukevics, E. *Chem. Heterocycl. Compd.* **2001**, *37*, 141–169.
(3) For cobalt-catalyzed nitrosation of α,β-unsaturated amides and esters leading to free oximes, see:(a) Kato, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2948–2953. (b) Kato, K.; Mukaiyama, T. *Chem. Lett.* **1990**, 1395–1398.
(4) An alternative synthesis would involve hydroformylation of olefin and subsequent condensation with hydroxylamine. Although examples of unactivated alkenes are known to undergo hydroformylation, controlling the regioselectivity represents a major concern. (a) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251–1259. (b) Ungvary, F. *Coord. Chem. Rev.* **2007**, *251*, 2087–2102. (c) Wiese, K.-D.; Obst, D. *Top. Organomet. Chem.* **2006**, *18*, 1–33. (d) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264–275. (e) Breit, B.; Seiche, W. *Synthesis* **2001**, *1*, 1–36.
(5) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519–4522.
(6) For prior work in this area from our own laboratory involving heterofunctionalization reactions of olefins, see:(a) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676–5677. (b) Waser, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099–4102. (c) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294–8295. (d) Waser, J.; González-Gómez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 4249–4252. (e) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712. (f) Gaspar, B.; Waser, J.; Carreira, E. M. *Synthesis* **2007**, *24*, 3839–3845. (g) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758–5760.
(7) (a) Kim, S.; Kim, S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809–822. (b) Kim, S.; Lim, C. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3265–3267. (c) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524–2526. (d) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190–12191. (e) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138–5139.
(8) Tröger, J.; Lux, E. *Arch. Pharm.* **1909**, 624–631.
(9) (a) Fontaine, P.; Chiaroni, A.; Masson, G.; Zhu, J. *Org. Lett.* **2008**, *10*, 1509–1512. (b) Jursic, B. S.; Douelle, F.; Bowdy, K.; Stevens, E. D. *Tetrahedron Lett.* **2002**, *43*, 5361–5365. (c) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumara, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831–2843.
(10) Experiments using $PhSiD_3$ with 4-phenylbutene (**2a**) showed complete d-incorporation at the terminal position. For details see the Supporting Information.
(11) (a) Fylaktakidou, K. C.; Hadjipavlov-Litina, D. J.; Litinas, K. E.; Varella, E. A.; Nicolaides, D. S. *Curr. Pharm. Des.* **2008**, *14*, 1001–1047. (b) Rheinheimer, J.; Rose, I.; Grote, T.; Lorenz, G.; Strathmann, S. German Patent No 19837794 A1, 2000. (c) Coviello, D. A.; Dvorin, S. L.; Greenberg, B. *J. Med. Chem.* **1972**, *15*, 94–95.
(12) Moriarty, R. M.; Chany II, C. J.; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478–2482.

JA904856K