ORGANIC LETTERS

2009
Vol. 11, No. 19
4358−4361

Highly Enantioselective and Regioselective Carbonyl Reduction of Cyclic α,β-Unsaturated Ketones Using TarB-NO_2 and Sodium Borohydride

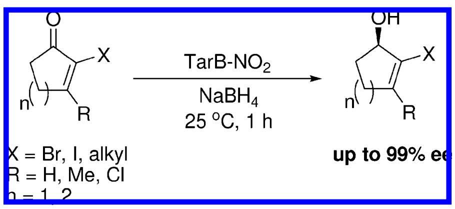
Jinsoo Kim, John Bruning, Kevin E. Park, David J. Lee, and Bakthan Singaram*

Department of Chemistry and Biochemistry, University of California Santa Cruz, 1156 High Street, Santa Cruz, California 95064

singaram@chemistry.ucsc.edu

Received July 22, 2009

ABSTRACT



Asymmetric 1,2-reduction of α,β-unsaturated ketones using TarB-NO_2 and $NaBH_4$ is reported. Simple cycloalkenones give products in low enantiomeric excess. However, cycloalkenones with α-substituents, such as halides, alkyl, and aryl, have been enantioselectively reduced with this system to yield chiral allylic alcohols in enantiomeric excess up to 99%. The starting materials for TarB-NO_2 are inexpensive, and the boronic acid can be easily recovered in high yield by a simple acid extraction.

The asymmetric carbonyl reduction of α,β-unsaturated ketones is a direct and simple method to synthesize chiral allylic alcohols. Enantioselective 1,2-reduction of these ketones is a valuable technique in the synthesis of allylic alcohols of synthetic interest.[1] However, selective 1,2-reduction is hampered by the competing 1,4-reduction and literature describing enantioselective 1,2-reduction is far surpassed by literature on asymmetric 1,4-additions.[2] Luche reported that the use of $CeCl_3$ and $NaBH_4$ in methanol exclusively gave 1,2-reduction products.[3] However, this method was never applied toward the asymmetric synthesis of allylic alcohols from the corresponding ketone. Modern syntheses that incorporate Luche reduction typically rely on nonreagent controlled factors to achieve enantioselectivity in their reductions.[4] Nutaitis reported the use of sodium triacetoxyborohydride ($NaBH(OAc)_3$) for the 1,2-reduction of 2-cyclohexen-1-one.[5] Although it proved effective for selective 1,2-reduction, it had not been applied for the asymmetric synthesis of chiral allylic alcohols. Modern methods describing the asymmetric 1,2-reduction of α,β-unsaturated ketones still remain scarce and often are limited to transfer hydrogenation.[6] Oxazaborolidines in stoichiomet-

(1) Vorogushin, A. V.; Wulff, W. D.; Hansen, H. -J. *Tetrahedron* **2008**, *64*, 949.
(2) (a) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; *Chapter 8D*, pp 569. (b) Prakash, G. S. K.; Wang, F.; Stewart, T.; Mathew, T.; Olah, G. A. *Proc. Nat. Acad. Sci. U.S.A.* **2009**, *106*, 4090. (c) Rabalakos, C.; Wulff, W. D. *Synlett* **2008**, 2826. (d) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524.
(3) Luche, J. -L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(4) (a) Hayashi, N.; Suzuki, T.; Usui, K.; Nakada, M. *Tetrahedron* **2009**, *65*, 888. (b) Gollner, A.; Mulzer, J. *Org. Lett.* **2008**, *10*, 4701. (c) Veitch, G. E.; Boyer, A.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 9402. (d) Pragani, R.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4613.
(5) Nutaitis, C. F.; Bernardo, J. E. *J. Org. Chem.* **1989**, *54*, 5629.
(6) (a) van Innis, L.; Plancher, J. M.; Marko, I. E. *Org. Lett.* **2006**, *8*, 6111. (b) Shirahata, T.; Sunazuka, T.; Yoshida, K.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Nagai, T.; Kiyohara, H.; Yamada, H.; Omura, S. *Tetrahedron* **2006**, *62*, 9483. (c) Garanger, E.; Boturyn, D.; Coll, J. -L.; Favrot, M. -C.; Dumy, P *Org. Biomol. Chem.* **2006**, *4*, 1958. (d) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walgrove, T.; Wills, M. *Tetrahedron* **2006**, 62–1864.

10.1021/ol901677b CCC: $40.75
Published on Web 08/27/2009

ric amounts have been used in 1,2-reduction to prevent alkene hydroboration.[7] DIP-chloride was reported in 1,2-reduction of 2-cyclohexen-1-one, but after 7 days the alcohol was isolated in only 36% ee.[8] Biotransformations using enzymes are perhaps the most common methods used in asymmetric 1,2-reduction of enones. Unfortunately, this method typically requires long reaction times and large excess of the enzyme performing the reduction.[9,10] Additionally, the α,β-unsaturated ketone must be soluble in water and usually only one enantiomeric alcohol can be synthesized by enzyme route. Chiral deprotonation of epoxides has been explored as an alternative route toward chiral allylic alcohols, but this method is also highly substrate limited.[11] Our interest in the asymmetric reduction of prochiral ketones using the chiral boronic ester TarB-NO_2 (Figure 1) and $NaBH_4$ prompted us to explore the asymmetric reduction of α,β-unsaturated ketones as a potential route to chiral allylic alcohols.

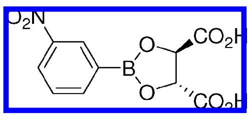
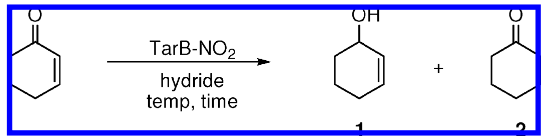


Figure 1. L-TarB-NO_2.

Our initial studies utilized $NaBH(OAc)_3$ as a stoichiometric reducing agent as this reagent had been reported to give predominantly allylic alcohol products.[12] We expected that substituting $NaBH_4$ with $NaBH(OAc)_3$ in TarB-NO_2 mediated reduction would allow us to enantioselectively reduce α,β-unsaturated ketones to the corresponding chiral allylic alcohols. We also included other reducing agents, such as $NaBH_4$, $NaBH(OPh)_3$, and $LiBH_3$(pyrrolidine). Accordingly, TarB-NO_2 was mixed in equimolar amounts with 2-cyclohexen-1-one and 2 equiv of the hydride source (Table 1). Initial reduction of 2-cyclohexen-1-one with TarB-NO_2 and $NaBH_4$ at room temperature gave a mixture of 2-cyclohexen-1-ol (**1**) and 2-cyclohexan-1-one (**2**) in a 25:75 ratio (entry 1) and the desired allylic alcohol was obtained in 33% ee. Reduction of the same ketone using $NaBH(OAc)_3$ at 0 °C for 12 h showed complete regioselectivity in the reduction, but the asymmetric induction was similar to that obtained with $NaBH_4$ (entry 2). Substitution of $NaBH(OAc)_3$ with $NaBH(OPh)_3$ led to a decrease in asymmetric reduction and a 80:20 mixture of **1** and **2** (entry 3). A recent publication described the use of $NaBH_4$ and boric acid in the selective 1,2-reduction of α,β-unsaturated ketones.[13] Although this method did favor 1,2-reduction in TarB-NO_2 mediated reaction with 2-cyclohexen-1-one, the amount of **2** was still significant and very little asymmetric induction was observed (entry 4). Previous research in our laboratory had demonstrated the ability of lithium aminoborohydride (LAB) reagents to selectively reduce the carbonyl of both α,β-unsaturated aldehydes and ketones.[14] However, in TarB-NO_2-mediated reduction lithium pyrrolidinoborohydride yielded a 75:25 mixture of **1** and **2** and nearly racemic alcohol (entry 5).

Table 1. TarB-NO_2-Mediated Reduction of 2-Cyclohexen-1-one[a]



entry	hydride	reaction temp (°C)/time	**1**:**2**[b]	% ee **1**[c]
1	$NaBH_4$	25/30min	25:75	33
2	$NaBH(OAc)_3$	0/12 h	100:0	33
3	$NaBH(OPh)_3$	0/12 h	80:20	17
4	$NaBH_4/B(OH)_3$	25/30min	87:13	6
5	$LiBH_3$(pyrrolidine)	25/3 h	75:25	6

[a] General reaction conditions: 1 mmol of ketone dissolved in 2 mL of 0.5 M TarB-NO_2 (1 mmol) followed by 2 mmol of hydride. [b] Ratio determined by GC. [c] Enantiomeric excess determined by chiral GC

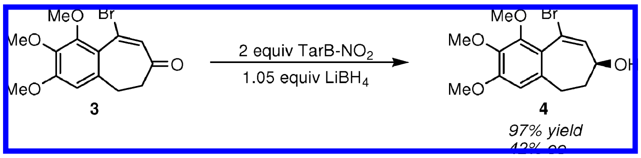
The low enantioselectivity in TarB-NO_2-mediated reduction of 2-cyclohexen-1-one led us to consider substrate modification to enhance asymmetric induction. Our computational modeling predicted that the transition state was lowest in energy when the carbonyl carbon was proximal to the carboxylic acid moiety of TarB-NO_2.[15] However, our model was unclear in delineating the influence of electronics and sterics in the asymmetric induction involving TarB-NO_2 mediated asymmetric reduction. Our recent work on asymmetric reduction of aliphatic ketones suggested that steric requirements of the alkyl groups attached to the carbonyl functionality were key in achieving high induction.[16] For example, the TarB-NO_2 mediated asymmetric reduction of 2-octanone gave the product alcohol in 60% ee whereas pinacolone, a ketone containing two sterically distinct alkyl groups, gave the product in 95% ee. We also noted that 2-methyl-3-pentanone gave product alcohol in 62% ee, similar to the results obtained with 2-octanone. Apparently, TarB-NO_2 reagent does not significantly distinguish an isopropyl group from an ethyl group.

In a recent report on the synthesis of allocolchicine analogues, TarB-NO_2−$LiBH_4$ was used in the reduction of ketone **3**.[1] However, the product alcohol **4** was obtained in

(7) Cho, B. T. *Tetrahedron* **2006**, *62*, 7621.
(8) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.
(9) Pollard, D. J.; Telari, K.; Lane, J.; Humphrey, G.; McWilliams, C.; Nidositko, S.; Salmon, P.; Moore, J. *Biotechnol. Bioeng.* **2006**, *93*, 674.
(10) Zagozda, M.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1958.
(11) (a) Oxenford, S. J.; Wright, J. M.; O'Brien, P.; Panday, N.; Shipton, M. R. *Tetrahedron Lett.* **2005**, *46*, 8315. (b) Gayet, A.; Andersson, P. G *Adv. Synth. Catal.* **2005**, *347*, 1242.
(12) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395.
(13) Cho, B. T.; Kang, S. K.; Kim, M. S.; Ryu, S. R.; An, D. K. *Tetrahedron* **2006**, *62*, 8164.
(14) Pasumansky, L.; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev.* **2006**, *10*, 959.
(15) Cordes, D. B.; Nguyen, T. M.; Kwong, T. J.; Suri, J. T.; Luibrand, R. T.; Singaram, B. *Eur. J. Org. Chem.* **2005**, 5289.
(16) Kim, J.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 3901.

42% ee (Scheme 1). It is possible that use of $NaBH_4$ would improve the asymmetric induction in this reduction as its insolubility in THF would minimize achiral reduction. It should be pointed out that neither the use of stoichiometric CBS catalyst in this reduction nor kinetic resolution of the alcohol with (−)-sparteine yielded the product allylic alcohol of higher optical purity.[17]

Scheme 1. Asymmetric Reduction of α,β-Unsaturated Ketones in the Synthesis of Allocolchinoids



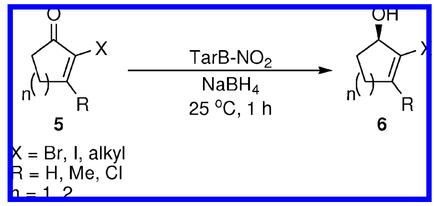
These results suggested that the reactions mediated by TarB-NO_2 are sensitive to steric requirements of the alkyl groups of the prochiral ketone. We envisioned that adding steric bulk to one of the α-carbons of a cyclic enone would improve the enantioselectivity of TarB-NO_2 mediated reductions. Initially we envisioned that 2-alkyl- or 2-arylcycloalkenones possess different steric requirements. However, these 2-substituted cyclohexenones are not available commercially, and their synthesis was not trivial. Consequently, we looked into 2-halocyclohexenones as possible substrates for TarB-NO_2/$NaBH_4$ system.

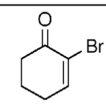
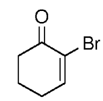
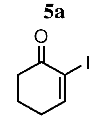
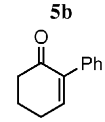
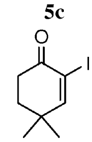
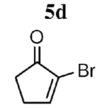
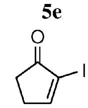
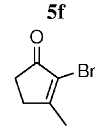
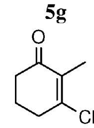
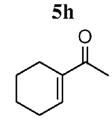
It is known that bromination of 2-cyclohexen-1-one followed by elimination with an amine base yields 2-bromo-2-cyclohexen-1-one **5a**.[18] The corresponding iodo analogue **5b** can be synthesized under Baylis−Hillman conditions with DMAP and molecular iodine.[19] We were gratified that the reduction of **5a** with TarB-NO_2 and $NaBH(OAc)_3$ yielded **6a** exclusively in 92% ee (Table 2, entry 1). Similarly, TarB-NO_2−$NaBH_4$ reduction of **5a** showed superb selectivity (99% ee) and excellent regioselectivity (entry 2). Typically these reductions were carried out by mixing 1 equiv of the enone with one equivalent of TarB-NO_2 followed by addition of 1.2 equiv of solid $NaBH_4$ in a single portion and stirring the reaction for 1 h at 25 °C. Results from the reduction of various cyclic α-substituted α,β-unsaturated ketones using TarB-NO_2 and $NaBH_4$ are summarized in Table 2. Both **5a** and **5b** showed exceptional enantioselectivity of 99% ee (entries 2 and 3). Suzuki coupling of phenylboronic acid with **5b** furnished 2-phenyl-2-cyclohexen-1-one (**5c**), which was reduced to the corresponding alcohol **6c** in 99% ee (entry 4).[20] High enantioselectivity was also observed with **5d**, which was reduced in 88% ee (entry 5). The cyclopentenone **5e** was reduced in excellent 94% ee (entry 6), and the β-substututed **5g** was reduced to afford the product alcohol in 92% ee (entry 9).

(17) Stoichiometric CBS-mediated reduction of the α-bromo-α,β-unsaturated ketone gave very high enantioselection.

(18) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088.
(19) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263.
(20) Felpin, F. -X. *J. Org. Chem.* **2005**, *71*, 8575.

Table 2. TarB-NO_2-Mediated Reduction of Cyclic α-Substituted α,β-Unsaturated Ketones (**5**)[a]



entry	ketone	% yield[b]	% ee (config)[c]
1[d]	 **5a**	-	92 (*R*)
2	 **5a**	50	99 (*R*)
3	 **5b**	68	99 (*R*)
4[e]	 **5c**	71	99 (*R*)
5	 **5d**	85	88 (*R*)
6	 **5e**	93	94 (*R*)
7	 **5f**	60	94 (*R*)
8		88	95 (*S*)
9	 **5g**	63	92 (*R*)
10	 **5h**	81	80 (*R*)[f]
11[g]	 **5i**	74	88 (*R*)

[a] General reaction conditions: 4 mmol of ketone dissolved in 8 mL of 0.5 M TarB-NO_2 (4 mmol) followed by 4.8 mmol of hydride. [b] Isolated yield. [c] Enantiomeric excess determined by chiral GC. Absolute configuration assigned by chiroptical comparison to literature values. [d] Reduction performed at 1 mmol scale using 2 equiv of $NaBH(OAc)_3$ as hydride. [e] 0.25 mmol scale reaction. [f] Configuration assigned by analogy. [g] Reduction performed at 0 °C.

One of the attractive aspects of TarB-NO_2-mediated reduction is the easy accessibility of either enantiomer of the product alcohol by simply switching (*S*,*S*)-tartaric acid for the (*R*,*R*)-isomer in the synthesis of TarB-NO_2. This is especially attractive since both isomers of tartaric acid are commercially available and are inexpensive. This is evidenced by the TarB-NO_2 mediated reduction of **5f** to either (*R*)- or (*S*)-**6f** in extremely high ee (entries 7 and 8). Additionally, the arylboronic acid of TarB-NO_2 can be easily recovered in high yield by a simple acid extraction.[21]

We also examined α-alkyl cyclic enone reductions with TarB-NO_2−$NaBH_4$. We were pleased to see that **5h** was reduced in high enantioselectivity, yielding alcohol **6h** in 80% ee (entry 10). Even the acyclic substrate **5i** yielded chiral alcohol in very good 88% ee (entry 11).

The asymmetric reduction of cyclic α-substituted α,*β*-unsaturated ketones shown in this report further demonstrates the versatility of TarB-NO_2. This challenging class of substrates was not only reduced with excellent regioselectivity, but the enantioselection was also very high. Apparently, TarB-NO_2 mediated reductions are highly controlled by the steric difference of the α-carbons of the ketone rather than electronic effects. One of the more appealing aspects of TarB-NO_2 is the simplicity in generating either enantiomer alcohol, the opposite isomer of tartaric acid can simply be used to synthesize TarB-NO_2. The synthesis of (*R*) alcohols from L-TarB-NO_2 and (*S*)-alcohols from D-TarB-NO_2 strongly suggests that these reactions occur according to our previously proposed reaction mechanism. Reaction conditions are mild, and reduction is typically complete in just 1 h. The starting materials are very inexpensive, and the boronic acid used to make TarB-NO_2 is easily recovered in high yield by an acidic extraction. Additionally, very little consideration needs to be taken with respect to the reagents; most can simply be weighed and added to a flask under inert atmosphere. The facile reaction conditions and high enantioselectivity make TarB-NO_2 a strong competitor in the field of asymmetric reduction.

(21) Eagon, S.; Kim, J.; Singaram, B. *Synthesis* **2008**, 3874.

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

OL901677B