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Mild and Expedient Asymmetric Reductions of α,β-Unsaturated Alkenyl and Alkynyl Ketones by TarB-NO_2 and Mechanistic Investigations of Ketone Reduction

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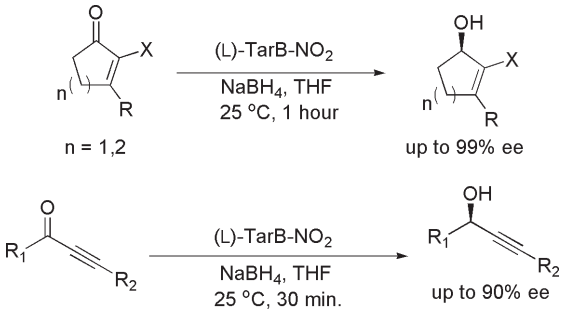

A facile and mild reduction procedure is reported for the preparation of chiral allylic and propargyl alcohols in high enantiomeric purity. Under optimized conditions, alkynyl and alkenyl ketones were reduced by TarB-NO_2 and $NaBH_4$ at 25 °C in 1 h to produce chiral propargyl and allylic alcohols with enantiomeric excesses and yields up to 99%. In the case of α,β-unsaturated alkenyl ketones, α-substituted cycloalkenones were reduced with up to 99% ee, while more substituted and acyclic derivatives exhibited lower induction. For α,β-ynones, it was found that highly branched aliphatic ynones were reduced with optimal induction up to 90% ee, while reduction of aromatic and linear aliphatic derivatives resulted in more modest enantioselectivity. Using the (L)-TarB-NO_2 reagent derived from (L)-tartaric acid, we routinely obtained highly enantioenriched chiral allylic and propargyl alcohols with (*R*) configuration. Since previous models and a reduction of a saturated analogue predicted propargyl products of (*S*) configuration, a series of new mechanistic studies were conducted to determine the likely orientation of aromatic, alkenyl, and alkynyl ketones in the transition state.

Introduction

The asymmetric reduction of prochiral alkenyl and alkynyl ketones is one of the most expedient methods to synthesize chiral allylic and propargyl alcohols. These chiral alcohols are present in a myriad of bioactive compounds and can be converted into a variety of synthetic intermediates due to the unique reactivities of the carbon−carbon double and triple bond. A handful of methods for the regiospecific 1,2-reduction of α,β-unsaturated alkenyl ketones have been reported, with one of the most popular being the cerium trichloride/sodium borohydride mediated Luche reduction.[1] Though the Luche reduction is not enantioselective, it has been used as a diastereoselective reduction agent for several recent compounds with modest success.[2] Modern enantioselective 1,2-reductions of α,β-unsaturated alkenyl ketones have been reported using several methods including ruthenium catalysts,[3] enzymes,[4] and the boron-containing DIP-Cl[5] and CBS[6] reagents. In the

(1) Luche, J. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(2) (a) Pragani, R.; Roush, W. *Org. Lett.* **2008**, *70*, 4613. (b) Gollner, A.; Mulzer, J. *Org. Lett.* **2008**, *70*, 4701. (c) Westermann, J.; Schneider, M.; Platzek, J.; Petrov, O. *Org. Process Res. Dev.* **2007**, *11*, 200. (d) Tsegay, S.; Huegal, H.; Rizzacasa, M. *Aust. J. Chem.* **2009**, *62*, 676. (e) Taber, D.; Gu, P.; Li, R. *J. Org. Chem.* **2009**, *74*, 5516.

(3) (a) Van Innis, L.; Plancher, J.; Marko, I. *Org. Lett.* **2006**, *8*, 6111. (b) Hannedouche, J.; Kenny, J.; Walsgrove, T.; Wills, M. *Synlett* **2002**, 263. (c) Peach, P.; Cross, D.; Kenny, J.; Mann, I.; Houson, I.; Campbell, L; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864.

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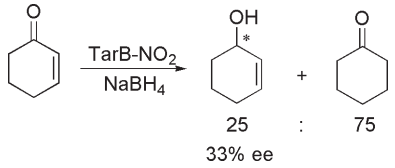
case of α,β-ynones, many of the early reagents used to reduce these substrates to highly enantioenriched propargyl alcohols were boron-based compounds, such as M. Midland's highly enantioselective reagent Alpine-Borane[7] (*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane), which continues to find modern synthetic applications.[8] Another early boron-based reagent reported to reduce ynones was the saccharide derived K-Glucoride reagent (potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidinene-5-deoxy-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]-nonane).[9] More recent asymmetric reduction reagents used with these substrates include ruthenium catalysts,[10] gallium catalysts,[11] and enzymes.[12]

Though there are many procedures for the reduction of α,β-unsaturated ketones to optically active allylic and propargyl alcohols, each has limitations. Heavy transition metals are often acutely toxic and their removal, especially in the preparation of pharmaceutical reagents, is not always trivial. Enzymatic reductions often require a water-soluble substrate and/or large excesses of microbial enzymes. Pinene-based boron reduction reagents such as Alpine-Borane and DIP-Cl also often require superstoichiometric quantities and extended reaction times to achieve maximal enantioselectivity. The advent of the CBS reagent provided a more convenient boron-mediated reduction procedure, but it often requires low temperatures (−78 °C), an excess of reagent, and/or modification of the borane source to achieve the best enantioselectivity and to avoid hydroboration of the alkene or alkyne. A Ru-BINAP transfer hydrogenation procedure has been reported by Noyori that can reduce unsaturated ketones without reduction or migration of the olefinic bond with good enantioselectivities for some cyclic and acyclic alkenyl ketones, but these catalysts were unable to reduce α,β-ynones.[13] Noyori, however, developed an alternative specialized family of ruthenium transfer hydrogenation catalysts that were able to reduce ynones to the corresponding propargyl alcohols with excellent asymmetric induction.[14]

Despite these preparative challenges, chiral allylic and propargylic alcohols remain extremely useful intermediates and are widespread throughout the synthetic literature. Chiral allylic alcohols have recently been prepared with enantioselective reduction agents from α,β-unsaturated ketones in a variety of recent syntheses including Mycorrhizin A,[15] cyclohexenyl nucleosides,[16] Symbiodinolide,[17] Brasilinolides,[18] and (+)-Spongistatin 1.[19] Chiral propargyl alcohols have also been used as intermediates in several recent syntheses, including (+)-Brefeldin,[20] Spicigerolide,[21] Balfilomycin A1,[22] Leiocarpin C, and (+)-Goniodiol.[23] Some bioactive molecules also contain chiral propargyl alcohols, such as the potent prostacyclin analogue Cicaprost and the antibacterial Uncialamycin.[24] The great utility of these reagents necessitates the search for improved methods for the enantioselective reduction of prochiral α,β-unsaturated alkenyl and alkynyl ketones.

SCHEME 1. Reduction of 2-Cyclohexene-1-one with TarB-NO_2 and $NaBH_4$



Results and Discussion

Reduction of α,β-Alkenyl Ketones. We first sought to investigate the reduction of cyclic α,β-unsaturated alkenyl ketones with TarB-NO_2 to see if we could achieve both good enantioselectivity and regioselectivity for 1,2-reduction to produce the chiral allylic alcohol.[25] When we reduced 2-cyclohexen-1-one with TarB-NO_2 and $NaBH_4$, we observed mainly the 1,4-reduction product cyclohexanone with the slightly enantioenriched 1,2-reduction product 2-cyclohexen-1-ol (Scheme 1).

We screened a variety of hydrides and discovered that by replacing $NaBH_4$ with $NaBH(OAc)_3$ we were able to isolate only the desired 1,2-reduction product. However, we were never able to achieve enantioselectivities above 33%. Previous reduction studies with TarB-NO_2 indicated that a large steric difference between the substituents flanking the carbonyl was required to achieve maximal induction.[26] To this end, we sought more functionalized substrates which could enhance the enantioselectivity of the reduction. Initially we

(4) (a) Musa, M.; Ziegelmann-Fjeld, K.; Vieille, C.; Zeikus, J.; Phillips, R. *J. Org. Chem.* **2007**, *72*, 30. (b) Polland, D; Telari, K.; Lane, J.; Humphrey, G.; McWilliams, C.; Nidositko, S.; Salmon, P.; Moore, J. *Biotechnol. Bioeng.* **2006**, *93*, 674. (c) Zagozda, M.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1958.
(5) Lovchik, M.; Goeke, A.; Frater, G. *J. Org. Chem.* **2007**, *72*, 2427.
(6) (a) Corey, E. J.; Bakshi, R.; Shibata, S.; Chen, C.; Singh, V. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Cho, B. T. *Tetrahedron* **2006**, *62*, 7621. (c) Holub, N.; Neidhofer, J.; Blechert, S. *Org. Lett.* **2007**, *9*, 513. (d) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917.
(7) Midland, M.; Tramontano, A.; Kazubski, A.; Graham, R.; Tsai, D.; Cardin, D. *Tetrahedron* **1984**, *40*, 1371.
(8) (a) Gopalsamuthriam, V.; Predeus, A.; Huang, R.; Wulff, R. *J. Am. Chem. Soc.* **2009**, *131*, 18018. (b) Desrat, S.; Weghe, P. *J. Org. Chem.* **2009**, *74*, 6728.
(9) Cho, B.; Park, W. *Bull. Korean Chem. Soc.* **1987**, *8*, 257.
(10) (a) Morris, D.; Hayes, A.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035. (b) Tanaka, K.; Shoji, T. *Org. Lett.* **2005**, *7*, 3561.
(11) (a) Ford, A.; Woodward, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 335. (b) Blake, A.; Cunningham, A.; Ford, A.; Teat, S.; Woodward, S. *Chem.—Eur. J.* **2000**, *6*, 3586.
(12) Schubert, T.; Hummel, W.; Kula, M.; Muller, M. *Eur. J. Org. Chem.* **2001**, 4181.
(13) (a) Ohkuma, T.; Ikehira, H.; Ikaria, T.; Noyori, R. *Synlett* **1997**, 467. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417.
(14) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
(15) Yu, B.; Jiang, T.; Quan, W.; Li, J.; Pan., X.; She, X. *Org. Lett.* **2009**, *11*, 629.
(16) Ferrer, E.; Alibes, R.; Busque, F.; Figueredo, M.; Font, J.; de March, P. *J. Org. Chem.* **2009**, *74*, 2425.
(17) Takamura, H.; Kadonaga, H.; Yamano, Y.; Han, C.; Kadota, I.; Uemura, D. *Tetrahedron* **2009**, *65*, 7449.
(18) Paterson, I.; Burton, P.; Cordier, C.; Housden, M.; Muhlthan, F.; Loiseleur, O. *Org. Lett.* **2009**, *11*, 693.
(19) Smith, A.; Sfouggatakis, C.; Risatti, C.; Sperry, J.; Zhu, W.; Doughty, V.; Tomoika, T.; Gotchev, D.; Bennett, C.; Sakamoto, S.; Atasoylu, O.; Shohei, S.; Bauer, D.; Takeuchi, M.; Makoto, J.; Sakamoto, Y. *Tetrahedron* **2009**, *65*, 6489.
(20) Kim, M.; Kim, H.; Tae, J. *Synlett* **2009**, *8*, 1303.
(21) Georges, Y.; Ariza, X.; Garcia, J. *J. Org. Chem.* **2009**, *74*, 2008.
(22) Kleinbeck, F.; Carriera, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 578.
(23) Yadav, J.; Premalatha, K.; Harshavardhan, S.; Subba Reddy, B. *Tetrahedron Lett.* **2008**, *49*, 6765.
(24) (a) Gais, H.; Kramp, G.; Wolters, D.; Reddy, L. *Chem.—Eur. J.* **2006**, *12*, 5610. (b) Skuballa, W.; Schillinger, E.; Sturzebecher, C.; Vorbruggen, H. *J. Med. Chem.* **1986**, *29*, 313. (c) Davies, J.; Wang, H.; Taylor, T.; Warabi, K.; Huang, X. *Org. Lett.* **2005**, *7*, 5233.
(25) Kim, J.; Brunigh, J.; Park, K.; Lee, D.; Singaram, B. *Org. Lett.* **2009**, *11*, 4358.
(26) (a) Eagon, S. C.; Kim, J.; Yan, K.; Haddenham, D.; Singaram, B. *Tetrahedron Lett.* **2007**, *48*, 9025. (b) Eagon, S. C.; Kim, J.; Singaram, B. *Synthesis* **2008**, *23*, 3874.

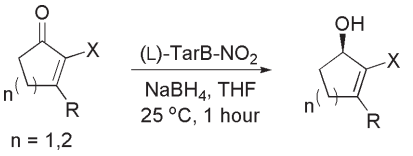
considered adding an alkyl or aryl substituent at the α-position of a cyclic alkenyl ketone, but such substrates are not commercially available and their synthesis is not straightforward. We did, however, find a simple procedure for the synthesis of 2-bromo-2-cyclohexen-1-one by reacting 2-cyclohexen-1-one with molecular bromine followed by triethylamine.[27] When we reduced this brominated compound with TarB-NO_2 and $NaBH(OAc)_3$, we were pleased to obtain the regioselective 1,2-reduction product in 92% ee. When we reduced the same compound with $NaBH_4$, we were pleased to again obtain only the 1,2-reduction product with 99% enantiomeric excess. Given the excellent reduction results we obtained using 2-bromo-2-cyclohexen-1-one, we prepared a variety of analogous substrates including α-substituted iodine derivatives under Baylis−Hillman conditions[28] and an α-substituted phenyl derivative using a Suzuki coupling.[29] The results of our reduction studies are summarized in Table 1.

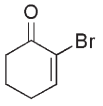
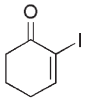
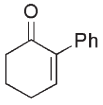
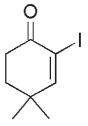
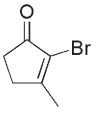
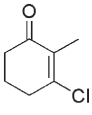
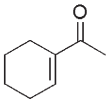
We were greatly pleased to find that all of our substrates were reduced with good to excellent enantioselectivity. All of the simple α-substituted cyclohexenones (Table 1, entries 1, 2, and 3) were reduced with a superb 99% enantiomeric excess. More highly substituted α,β-unsaturated cyclohexenones were also reduced with good enantioselectivity by TarB-NO_2 (Table 1, entries 4 and 8). In addition to cyclohexenone derivatives, we also investigated several α-substituted α,β-unsaturated cyclopentenones and were pleased to find that all were reduced with greater than 90% enantioselectivity (Table 1, entries 5−7). We investigated the reduction of some acyclic α,β-unsaturated ketones, but unfortunately achieved very poor induction for these substrates. However, an α-alkyl cyclic enone was reduced by TarB-NO_2 with good enantioselectivity (Table 1, entry 9). It should also be noted that we routinely recovered the (*R*)-allylic alcohol when using (L)-TarB-NO_2. Given our promising results with cyclic α,β-unsaturated alkenyl ketones, we wished to next extend our investigation to alkynyl derivatives.

Reduction of α,β-Unsaturated Alkynyl Ketones. Several α,β-ynones were prepared by adding the appropriate aldehyde to a 1 M solution of the lithiated terminal alkyne in THF at 0 °C under a dry and inert atmosphere. The racemic product was then oxidized with pyridinium chlorochromate (PCC) in DCM to give the desired substrate. The ynone 5-phenyl-4-butyn-3-one, however, was obtained commercially and used without further purification. Optimization studies indicated that 1 equiv of TarB-NO_2 at room temperature gave optimal results when reduced with sodium borohydride. ^{11}B NMR analysis of the reaction mixture also confirmed that there was no hydroboration of the alkyne during the reaction. Using this optimized procedure, we reduced a variety of α,β-ynones with (L)-TarB-NO_2. The results are summarized in Table 2.

The selectivity of the reaction was found to be highly dependent upon the steric bulk of the nonalkynyl group attached directly to the ketone. Methyl and ethyl alkynyl ketones were reduced with little or no enantioselectivity, but isopropyl and cyclohexyl alkynyl ketones were reduced with enantioselectivities from 75% to 83% (Table 2, entries 5−7). *tert*-Butyl alkynyl ketones were reduced with the best enantioselectivity up to a maximum of 90% ee for 2,2-dimethyl-non-4-yn-3-one (Table 2, entry 10). This preference for highly branched aliphatic alkynyl

TABLE 1. Reduction of α,β-Unsaturated Ketones with (L)-TarB-NO_2[a]

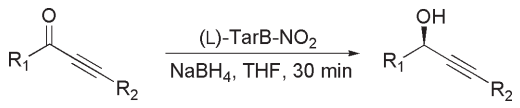


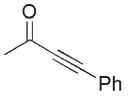
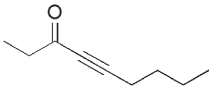
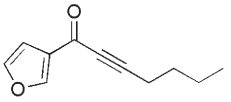
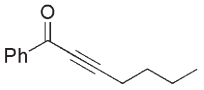
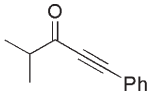
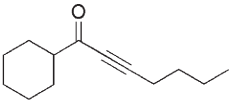
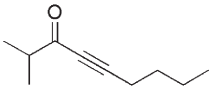
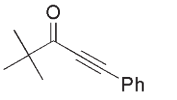
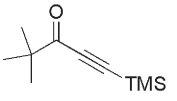
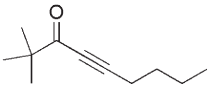
entry	ketone	yield (%)	% ee[b]	config.[c]
1		50	99	(*R*)
2		68	99	(*R*)
3		71	99	(*R*)
4		85	88	(*R*)
5		93	94	(*R*)
6		60	94	(*R*)
7		63	92	(*R*)
8		81	80	(*R*)[d]
9		74	88	(*R*)

[a]Standard reaction carried out under argon on a 4 mmol scale with 1.2 equiv of $NaBH_4$. [b]Determined by GC analysis of the acetylated alcohols on a Supelco Beta-Dex 120 column. [c]Assigned by comparison to the literature value. [d]Assigned by analogy.

(27) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088.
(28) Krafft, M. E.; Cran, J. W. *Synlett* **2005**, 1263.
(29) Felpin, F. X. *J. Org. Chem.* **2005**, *70*, 8575.

TABLE 2. Reductions of Ynones with (L)-TarB-NO_2



entry	ketone	yield (%)	% ee[a]	config.
1		91	6	-[b]
2		99	20	-[b]
3		99	33	(*R*)[c]
4		92	58	(*R*)[c]
5		65	75	(*R*)[d]
6		73	80	(*R*)[d]
7		74	83	(*R*)[d]
8		69	84	(*R*)[d]
9		87	85	(*R*)[d]
10		96	90	(*R*)[d]

[a]Determined by GC analysis of the acetylated alcohols on a Supelco Beta-Dex 120 column. [b]Observed rotation value too small to accurately measure. [c]Assigned by analogy. [d]Assigned by comparison to the literature value. See the Supporting Information.

ketones by a boron-based reduction reagent was previously observed with the popular DIP-Cl reagent.[30] Interestingly, aromatic and heteroaromatic substituents bound to the ketone gave markedly depressed enantioselectivities when compared

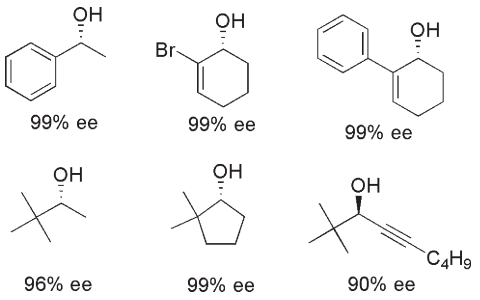


FIGURE 1. Chiral alcohols obtained with (L)-TarB-NO_2.

to branched aliphatic substrates (Table 2, entries 3 and 4). Varying the size of the group attached on the alkyne distal to the ketone seemed to have a limited effect, with larger groups slightly reducing the enantioselectivity of the reaction. Also, we were able to compare the optical rotation of several of our products to those previously reported in the literature and found that all were of the (*R*) configuration. Though TarB-NO_2 achieved poor reduction with unhindered *n*-alkyl alkynyl ketones, these substrates have been successfully reduced with high enantioselectivity by a modified CBS reagent.[31] The NB-Enantrane and Alpine-Borane reagents have also demonstrated excellent stereoselectivity when reducing unhindered *n*-alkyl alkynyl ketones.[7,32] This makes TarB-NO_2 mediated reductions of hindered alkyl alkynyl ketones complementary to the reduction of unhindered analogues by these other popular boron-based reagents.

Mechanistic Implications. We were pleased to find that like previously investigated aromatic and aliphatic substrates, (L)-TarB-NO_2 was able to reduce a variety of α,β-unsaturated alkenyl and alkynyl ketones with excellent induction (Figure 1).

(L)-TarB-NO_2 mediated reductions of these substrates consistently resulted in products of (*R*) configuration as determined by the observed optical rotation in comparison to previously published literature values.[26] Given the symmetry of the TarB-NO_2 reagent, these products are assumed to arise from one of the four most likely transition states determined by the coordinating lone pair of the substrate ketone and the face of the substrate carbonyl presented to the active hydride. These transition states (TS), with arbitrary conformations of the aromatic groups, are shown in Figure 2.

We previously published ab initio calculations modeling the transition state of TarB-NO_2 based on early results with the reduction of prochiral ketones and the results suggested an orientation consistent with TS(**I**).[33] The optical rotation values corresponding to products of the (*R*) configuration for previously investigated aromatic and aliphatic substrates had always agreed with the configuration predicted from this model (Figure 3).

In the case of acetophenone, the absolute configuration of the product alcohol arises from a *si*-face attack corresponding to either TS(**I**) or TS(**II**). This initial model, however, was greatly simplified to reduce computation time and as such

(30) Brown, H. C.; Ramachandran, V. *Acc. Chem. Res.* **1992**, *25*, 16.

(31) Helal, C.; Magriotis, P.; Corey, E. *J. Am. Chem. Soc.* **1996**, *118*, 10938.

(32) Brown, H. C.; Pai, G. *J. Org. Chem.* **1985**, *50*, 1384.

(33) Cordes, D.; Nguyen, T.; Kwong, T.; Suri, J.; Luibrand, R.; Singaram, B. *Eur. J. Org. Chem.* **2005**, 5289.

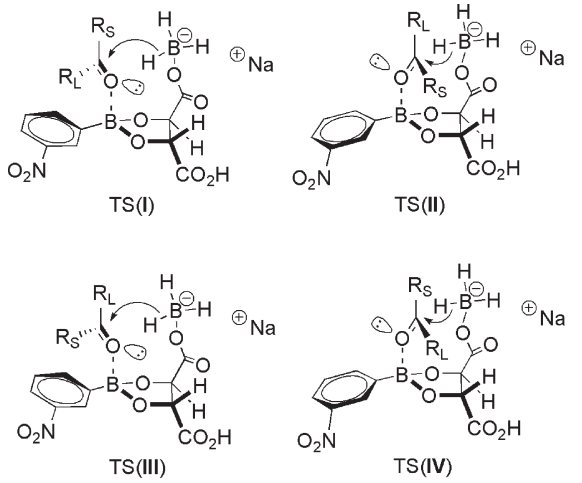


FIGURE 2. Likely transition states for reduction with (L)-TarB-NO_2.

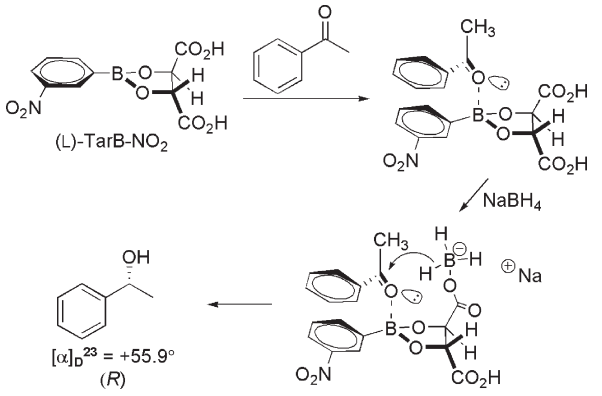


FIGURE 3. Previously published transition state model with acetophenone corresponding to TS(**I**).

did not account for steric or solvent effects, nor did it contain any aromatic rings. The limitations of the model soon became apparent given our results with α,β-unsaturated alkenyl and alkynyl ketones. When the α-substituted cyclic α,β-unsaturated ketone 2-phenylcyclohex-2-enone (Table 1, entry 3) is reduced with (L)-TarB-NO_2, the corresponding (*R*) alcohol is obtained with a 99% enantiomeric excess. The absolute configuration of the product, as determined from the optical rotation value, results from a *si*-face attack of the hydride consistent with TS(**I**) and TS(**II**). However, when modeling these two options, it is readily apparent that TS(**I**) would have significant steric repulsion (Figure 4).

In addition to the questions raised by the reduction of α,β-unsaturated alkenyl ketones, our model of TS(**I**) predicted the absolution configuration of our propargyl alcohols to be (*S*). In fact, when we compared the optical rotation of our products to those previously reported in the literature, we found that all were of the (*R*) configuration (Table 2). Again, it should be noted that our original computational model was greatly simplified to reduce calculation time. Given these contradictory results and the limitations of our initial computational model, we decided to conduct a more detailed mechanistic investigation of TarB-NO_2 mediated reductions.

The reduction of acetophenone by (L)-TarB-NO_2 was selected first for investigation since the product (*R*)-alcohol

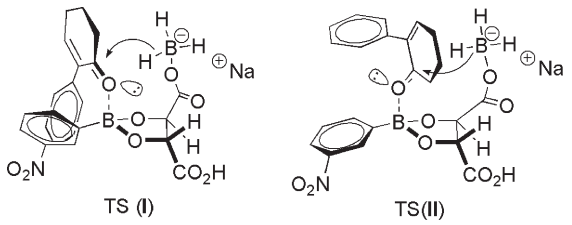


FIGURE 4. Transition state models for the reduction of 2-phenylcyclohex-2-enone. Given the fact that the absolute configuration of the product dictates that the carbonyl *must* orientate the *si*-face of the carbonyl toward the acyloxyborohydride, it is highly unlikely that the phenyl ring of the ketone substrate is positioned immediately adjacent to the TarB-NO_2 aromatic ring as per TS(**I**).

is obtained with a 99% ee and the phenyl ring is a convenient fluorophore. The absolute configuration of the product dictates that the hydride must be delivered to the *si*-face of the ketone consistent with either TS(**I**) or TS(**II**). If TS(**I**) was indeed the preferred orientation for this substrate, the close proximity of the two aromatic rings of TarB-NO_2 and acetophenone suggested the possibility of a $\pi-\pi$ stacking interaction. To elucidate whether or not such stacking could be observed, a UV spectrum was obtained for a THF solution of (L)-TarB-NO_2, acetophenone, and a mixture of both. The resultant spectrum of the (L)-TarB-NO_2 and acetophenone mixture displayed neither a shift in the observed λ_{max} values, the appearance of new absorption peaks, nor any temperature dependence—the standard hallmarks of π-stacking interactions.[34] Additionally, we examined the ^{1}H NMR spectrum of a 1:1 (L)-TarB-NO_2/acetophenone mixture for the characteristic upfield shift of aromatic protons in $\pi-\pi$ systems, but we observed no change in the observed ppm values for any of the aromatic signals.[35] These results all indicate that no significant $\pi-\pi$ interactions are present between the TarB-NO_2 reagent and acetophenone.

Though we found no direct evidence for π-stacking interactions that could arise from TS(**I**), this could be due to the fact that the ketone substrate is known to be only weakly bound to the TarB-NO_2 substrate in THF as evidenced by ^{11}B NMR studies. This could also be due to the fact that an aromatic ring bearing a nitro group and another ring bearing a carbonyl make poor partners for $\pi-\pi$ interactions. To make a more tightly bound model, we prepared the product-like analogue boronate **1** in situ as per Scheme 2.

Formation of **1** was confirmed by the shift observed in the ^{11}B NMR spectra, as well as the ^{1}H NMR downfield shift of the methine proton on the 1-phenylethanol moiety. More notably, the aromatic signals for both the 1-phenylethanol and TarB-NO_2 phenyl ring in **1** were identical to the signals observed for the free compounds, again suggesting that no significant π-stacking interactions are present. It should be noted that while boronate **1** may approximate the stable configuration of the final product, it does not necessarily approximate the active transition state that leads to the experimentally observed products since the most stable complex does not necessarily arise from the most reactive one as per the Curtin−Hammett principle. However, these solution-phase analogues can provide valuable insight into constructing a better mechanistic model for TarB-NO_2

(34) Swager, T. M.; Song, C. *Org. Lett.* **2008**, *10*, 3575.
(35) Martin, R. B. *Chem. Rev.* **1996**, *96*, 3043.

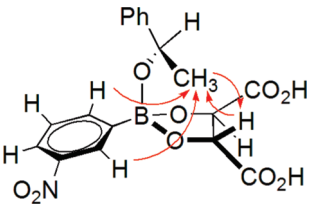
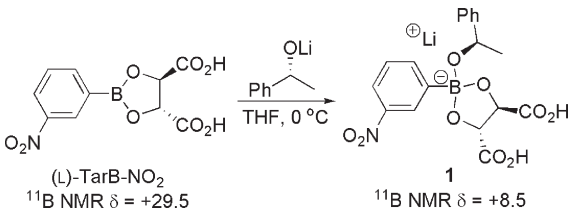


FIGURE 5. Selected NOESY interactions for **1**.

SCHEME 2. Preparation of Boronate 1



mediated reductions. Specifically, the lack of any evidence for $\pi-\pi$ interactions in **1** suggests that other geometrical and/or steric effects are responsible for the induction achieved with TarB-NO_2.

We next decided to investigate whether correlation spectroscopy could provide additional evidence for either TS(**I**) or TS(**II**) in the reduction of acetophenone. When we attempted to acquire NOESY spectra of a (L)-TarB-NO_2/acetophenone mixture, we did not observe any through-space interactions, again likely due to the weak association of the substrate to TarB-NO_2 in a THF solution. As an alternative, we decided to substitute boronate **1** prepared in situ and perform a series of NOESY experiments (Figure 5).

Irradiation of the methine and ortho protons of TarB-NO_2 all displayed through-space coupling to the methyl protons on the phenylethanol moiety of **1**. Irradiation of phenylethanol methyl protons also resulted in coupling to the methine protons on the tartrate backbone of TarB-NO_2. Additionally, when the aromatic protons of the phenylethanol moiety are irradiated, no NOE effects are observed. Since NOE interactions are generally not observed beyond 4 Å, the observed interactions suggest that, in terms of **1**, the aromatic ring of the phenylethanol is positioned away from the TarB-NO_2 while the methyl group is close to the dioxoborolane ring of TarB-NO_2. Such a configuration would be consistent with either TS(**II**) or TS(**III**). Given that the observed absolute configuration of the product can only arise from a *si*-face attack represented by TS(**I**) and TS(**II**), these results suggest that TS(**II**) is the most likely orientation for reduction.

Having examined the evidence for the reduction of acetophenone, we next turned our attention to alkynyl ketones. Since the optical rotation values of six of our chiral propargyl alcohols had been previously reported and all were of the (*R*) configuration, we were confident in our assignment of the absolute configuration of the products. We suspected that the alkyne triple bond was responsible in some manner for the apparent inversion of configuration. To test this hypothesis, we prepared an alkane analogue of one of our alkynyl ketones and reduced it with (L)-TarB-NO_2 (Figure 6). The striking result confirmed that the

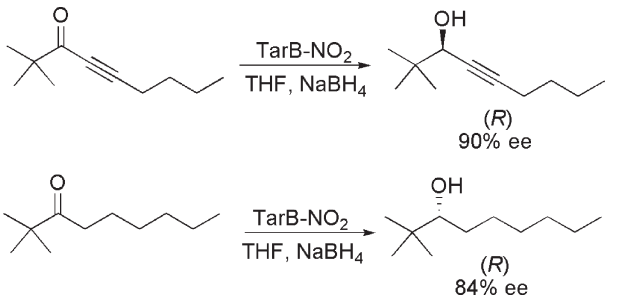


FIGURE 6. Comparative reduction of an alkyl and alkynyl ketone with TarB-NO_2.

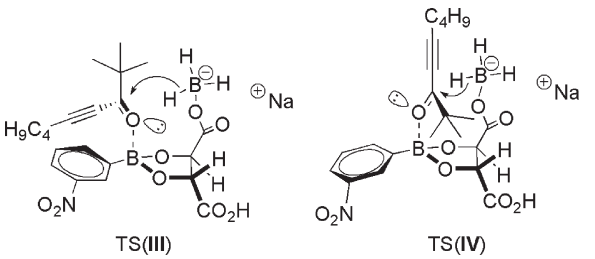
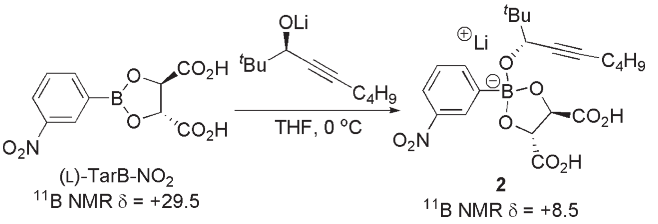


FIGURE 7. Likely transition states for the reduction of alkynyl ketones with TarB-NO_2. From a sterics standpoint, it would be more reasonable to expect the *tert*-butyl group to be positioned above and away from the TarB-NO_2 reagent corresponding to TS(**III**) rather than directly above the dioxoborolane ring of TarB-NO_2 as in TS(**IV**). Nevertheless, we decided to look for additional experimental evidence supporting either TS(**III**) or TS(**IV**).

SCHEME 3. Preparation of Boronate 2



presence of the triple bond was responsible for the observed inversion of configuration.[36]

The absolute configuration of the product propargyl alcohol indicated that the alkyne was presenting the opposite face of the carbonyl to the active acyloxyborohydride of TarB-NO_2. Such a configuration would require an orientation consistent with either TS(**III**) or TS(**IV**). The remaining question was whether the sterically demanding *tert*-butyl group was positioned above the TarB-NO_2 reagent as with the phenyl ring of acetophenone, or if the alkyne was positioned above the TarB-NO_2 reagent (Figure 7).

To gain a better understanding of the orientation of the transition state for the reduction of alkynyl ketones, we decided to create the new boronate **2**. Formation of the new compound in situ was confirmed by both ^{1}H and ^{11}B NMR (Scheme 3).

To test for any interactions between the alkyne and aromatic π systems, the UV spectra of both **2** and an alkane

(36) Note that the alkyne group has a higher priority than the *tert*-butyl group under the Cahn−Ingold−Prelog convention.

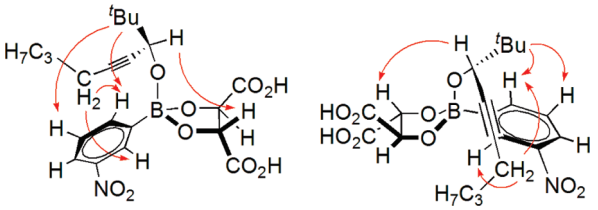


FIGURE 8. Selected NOESY and ROESY correlations for **2**.

analogue were obtained. Both spectra were identical, suggesting no such interactions were present. We next took **2** and performed several NOESY and ROESY experiments, the results of which are summarized in Figure 8.

A strong correlation was observed between the methine proton of the propargyl alcohol and the methine proton on the backbone of the dioxoborolane ring of the TarB-NO_2 reagent, suggesting the conformer depicted above. More importantly, however, was an interaction observed between the methylene protons of the aliphatic carbon bonded to the alkyne and the ortho protons on TarB-NO_2. This suggested that in terms of boronate **2**, the alkyne was relatively close to the aromatic ring of TarB-NO_2. If this orientation holds true for the coordination complex between α,β-ynones and TarB-NO_2, it would suggest a conformation consistent with TS(**III**). Such a conformation would imply that α,β-ynones coordinate to TarB-NO_2 with the sterically demanding group in the same position as with other aromatic and aliphatic substrates, but presents the opposite face of the carbonyl for reduction by the active hydride when compared to TS(**II**). Since we have already shown that the alkyne alone is responsible for this change in coordination configuration, we believe that this is due either to the electronic properties or the hybridization peculiar to the carbon−carbon triple bond.

Spectroscopic studies of the reduction of aromatic and alkynyl ketones demonstrated that TS(**I**), indicated as the active reducing species by earlier computational studies, was not sufficiently accurate to predict the observed configuration of the product alcohols. NMR studies of product-like boronate analogues suggested that TS(**II**) could explain the absolute configuration of the product alcohols obtained from the reduction of aromatic, aliphatic, and α,β-unsaturated cyclic ketones. α,β-Ynones, however, are thought to assume an orientation consistent with TS(**III**).

To further develop a more accurate model, a series of new ab initio computational studies were performed to model the previously published transition state as well as the reduction of acetophenone and an α,β-ynone. All calculations were performed with the GAMESS software suite[37] utilizing unconstrained geometry optimizations, double-differenced seminumerical nuclear Hessian calculations, and intrinsic-reaction coordinate calculations preformed with the (R)PBE0 hybrid density functional[38] and the 6-31G(d) basis.[39] In addition, s,p-diffuse functions[40] were added to all boron and oxygen atoms, as well as the carboxylate carbon of TarB-X and the carbonyl carbon of the ketone substrate. To aid in computation, a TarB-NO_2 analogue was utilized with the nonparticipating carboxylic acid and nitro group removed.

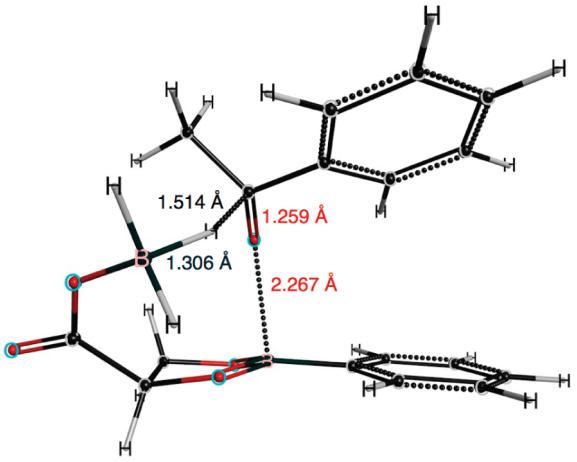


FIGURE 9. Calculated transition state for the reduction of acetophenone.

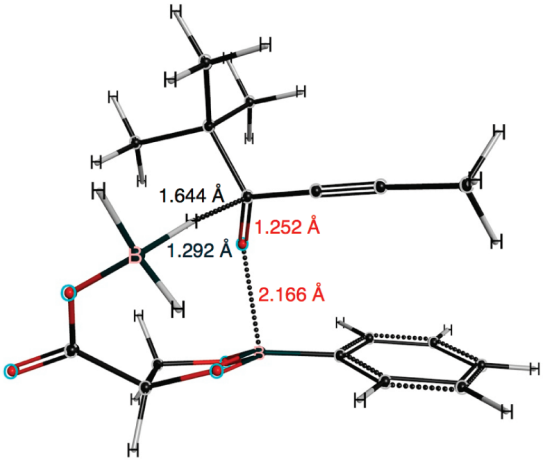


FIGURE 10. Calculated transition state for an α,β-ynone.

When the originally published transition state was recalculated with the above parameters, it was found that the previous model was highly unstable and strongly favored dissasociation. In fact, in the absence of the sodium atom the previously published transition state completely disassociates. Under our computational parameters, we also found that substrate and TarB-NO_2 favor disassociation, in agreement with ^{11}B NMR studies. However, when the reduction of acetophenone was calculated, it was found that the attack of the hydride from the *si*-face, resulting in the experimentally observed (*R*) product, was energetically perferred by 1.62 kcal/mol (Figure 9).

The newly calculated transition state indicated an early transition state wherein the hydride delivery occurs before a formal coordination is established between the substrate ketone and TarB-NO_2. Since the calculations were performed in the absence of molecular motion (0 K) in the gas phase and the hydride delivery occurs before coordination, the orientation of the substrate ketone does not conform directly to previously modeled transition states for TarB-NO_2 reductions performed in THF at room temperature. However, these studies confirm on an ab initio basis that a

(37) Schmidt, M.; Baldridge, K.; Boatz, A.; Elbert, S.; Gordon, M.; Jensen, J.; Koseki, S.; Matsunaga, N.; Nguyen, K.; Windus, T.; Dupuis, M.; Montgomery, J., Jr. *J. Comput. Chem.* **1993**, *14*, 1347.
(38) Adamo, C.; Barone, V. *J. Chem. Phys.* **1999**, *110*, 6158.
(39) Hehre, W.; Ditchfield, R.; Pople, J. *J. Chem. Phys.* **1972**, *56*, 2257.
(40) Frish, M.; Pople, J.; Binkley, J. *J. Chem. Phys.* **1984**, *80*, 3265.

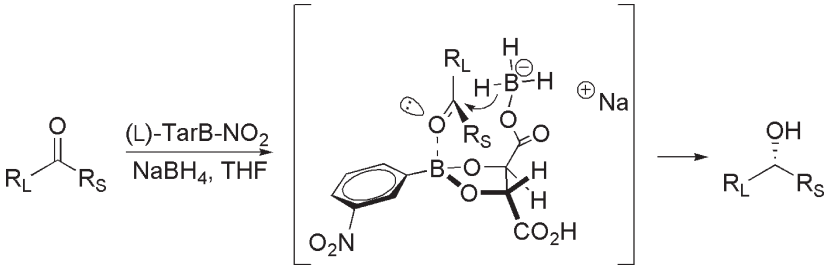


FIGURE 11. Proposed transition state for ketone reduction with (L)-TarB-NO_2.

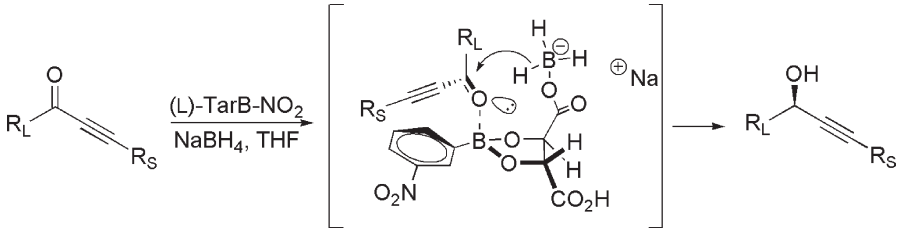


FIGURE 12. Proposed transition state for α,β-ynone reduction with (L)-TarB-NO_2.

si-face hydride delivery is energetically favored in the case of acetophenone, resulting in the experimentally observed product.

Following the calculation of the transition state for acetophenone, the same parameters were used to calculate the reduction of an α,β-ynone. It was found that the ynone presents the opposite face of the substrate carbonyl to the approaching hydride in the energetically preferred transition state, in agreement with spectroscopic and experimental results (Figure 10).

The calculated transition state for the alkynyl ketone also indicated an early transition state where hydride delivery occurs before a full coordination between the substrate and TarB-NO_2 and thus does not directly correspond to previously modeled transition states. Most importantly, however, this result confirms on an ab initio basis that an α,β-alkynyl ketone energetically prefers a different orientation than that of acetophenone, which leads to the experimentally observed product.

Conclusion

We have reported a facile room temperature boron-mediated reduction procedure for producing highly enantioenriched allyl and propargyl alcohols using $NaBH_4$ as the hydride source. Reductions of α-substituted α,β-unsaturated cyclic alkenyl ketones and α,β-ynones with TarB-NO_2 proceed smoothly and quickly under mild conditions at room temperature, producing chiral alcohols of up to 99% ee with isolated yields up to 99%. For α,β-unsaturated alkenyl ketones, α-substituted cycloalkenones exhibited the highest induction, while α,β- and α,γ-substituted derivatives exhibited slightly lower enantioselectivity. In the case of α,β-ynones, it was found that highly branched aliphatic ynones were reduced with optimal induction, while reduction of aromatic and linear aliphatic derivatives resulted in more modest induction. Results obtained from spectroscopic and ab initio experiments indicated that most substrates are likely reduced via the transition state depicted in Figure 11.

Though this transition state was not directly observed in solution; spectroscopic, calculational, and experimental evidence suggest that this is the most likely orientation of the substrate ketone with TarB-NO_2. Regardless of the ultimate accuracy of this proposed transition state, the new model for reduction correctly predicts the observed absolute configuration of alcohols obtained without assuming sterically crowded, high-energy configurations as predicted by the previous model. Reductions with α,β-ynones is an exception, however. Ab initio, experimental, and spectroscopic studies suggest that these substrates are likely reduced via a different transition state, shown in Figure 12.

The ability of TarB-NO_2 to prepare highly enantioenriched secondary alcohols from α,β-unsaturated ketones in 1 h at room temperature with $NaBH_4$, coupled with more accurate mechanistic models for the prediction of product configuration make it a highly effective tool for the asymmetric reduction of prochiral ketones.

Experimental Section

Preparation of (L)-TarB-NO_2. A 500-mL round-bottomed flask with a side arm and a stir bar was oven-dried, cooled under argon, and charged with 3-nitrophenylboronic acid (20.04 g, 120 mmol), (L)-tartaric acid (18.00 g, 120 mmol), and CaH_2 (10.10 g, 240 mmol), sealed with a septum, and fitted with a reflux condenser. Dry THF (240 mL) was added slowly through the side arm and the system was refluxed for 1 h followed by cooling. The suspension was cannulated with argon from the sealed reaction vessel to a sealed medium frit attached to a dry flask to remove calcium salts. The clear, yellow-brown solution was then transferred via cannula to a dry ampule as a 0.5 M solution in THF. ^1H NMR indicates the yield was 99%. TarB-NO_2 solutions were stored in sealed ampules at room temperature and kept away from light. These stock solutions are stable for as long as one year. (Note: TarB-X reagents are moisture-sensitive. Air-sensitive techniques and dry glassware should be used in their preparation and application.)

Procedure for the Reduction of α,β-Unsaturated Ketones with TarB-NO_2. An oven-dried 100-mL round-bottomed flask equipped with a stir bar was sealed with a septa and cooled under argon. The flask was charged with TarB-NO_2 (8 mL of a 0.5 M solution in THF, 4 mmol) and the ketone (4 mmol). The solution was stirred for 15 min after which solid $NaBH_4$ (0.18 g, 4.8 mmol) was added directly causing vigorous evolution of H_2 gas. The

solution was allowed to stir for 1 h. The reaction was quenched dropwise by the addition of H_2O (10 mL) and the mixture was brought to pH 12 with 3 M NaOH (5 mL). The solution was extracted with Et_2O (3 × 20 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to isolate the product alcohol.

Preparation of α,β-Ynones:. The Preparation of 2-Methynon-4-yn-3-one Is Representative An oven-dried 50-mL round-bottomed flask equipped with a stir bar was sealed with a septa and cooled under argon. A 20 mL sample of dry THF was transferred to the flask. The flask was then cooled over an ice bath. 1-Hexyne (2.30 mL, 20 mmol) was added to the flask, followed by the dropwise addition of *n*-BuLi (8.0 mL of a 2.5 M solution in hexanes, 20 mmol). The mixture was stirred for 15 min, then butyraldehyde (1.83 mL, 20 mmol) was added slowly to the reaction mixture. The reaction was stirred an additional 30 min. The ice bath was then removed and the reaction was quenched with 2 mL of MeOH. The mixture was then transferred to a separatory funnel and diluted with 45 mL of a 2:1 ethyl ether/pentanes mixture. The organic layer was washed with 1 M HCl (2 × 20 mL), 1 M NaOH (2 × 20 mL), then D.I. water (1 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield the product as a colorless or slightly yellow oil (2.74 g, 17.8 mmol, 89% yield). The crude product was then transferred to an oven-dried 100-mL round-bottomed flask equipped with a stir bar and diluted in enough DCM to obtain approximately a 0.25 M solution (70 mL). To this solution was added 1.5 equiv of PCC (5.76 g, 26.7 mmol) and the solution was allowed to stir for 16 h. The DCM was removed under reduced pressure, then pentanes (50 mL) and Celite (~2 g) were added to the flask and the solution was stirred vigorously for 30 min, or until the chromium salts were free-flowing in the solution. The suspension was then filtered through a Buchner funnel to remove the salts. The remaining pentane layer was evaporated under reduced pressure to yield the product 2-methylnon-4-yn-3-one (1 g) as a colorless oil (1.96 g, 12.8 mmol, 72% yield).

Procedure for the Reduction of Ynones with TarB-NO_2:. The Reduction of 2-Methylnon-4-yn-3-one Is Representative A 25-mL oven-dried round-bottomed flask was equipped with a stir bar and cooled under argon. The flask was charged with TarB-NO_2 (6 mL of a 0.5 M solution in THF, 3 mmol) and 2-methylnon-4-yn-3-one (1 g) (0.454 g, 3 mmol). The ketone and TarB-NO_2 were stirred for 15 min after which $NaBH_4$ (0.227 g, 6 mmol) was added directly to the solution causing vigorous evolution of H_2 gas. The mixture was allowed to stir for 30 min. The solution was quenched dropwise with 1 M HCl until gas evolution ceased. The mixture was brought to pH 12 with 3 M NaOH and stirred for 30 min. The solution was extracted with a 2:1 ether/pentane mixture (3 × 10 mL). The combined organic layers were then washed with 3 M NaOH (2 × 10 mL), 1 M HCl (2 × 10 mL), and D.I. water (1 × 10 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain the product 2-methylnon-4-yn-3-ol (2 g) as a light amber oil (0.347 g, 2.25 mmol, 75% yield). The enantiomeric excess of the acetylated alcohol was determined by GC on a Supelco β-cyclodextrin 120 column (30 m × 0.25 mm). To recover the arylboronic acid, the combined aqueous layers were acidified with concd HCl to pH 1 and extracted with diethyl ether (3 × 10 mL). The combined organic layers are washed quickly with a small amount of sat. NaCl solution (5 mL) and dried over MgSO4. Evaporation under reduced pressure yields the phenylboronic acid as an off-white flakey solid, which was stored in a desiccator.

Preparation of Boronate (1). A 25-mL oven-dried round-bottomed flask was equipped with a stir bar and cooled under argon. Dry THF (3.08 mL) was added to the flask, followed by (*R*)-1-phenylethanol (0.242 mL, 2 mmol). The solution was then cooled over an ice bath under argon. *n*-BuLi (0.83 mL of a 2.4 M solution in hexanes, 2 mmol) was then added dropwise to the solution. Once the addition was complete, the ice bath was removed and the solution was allowed to warm to room temperature (15 min.). A solution of TarB-NO_2 (4 mL of a 0.5 M solution in THF, 2 mmol) was then added dropwise to the flask. After 30 min of stirring, an aliquot (700 μL) was transferred to a sealed NMR tube for ^{11}B NMR analysis to confirm formation of the product (160.4 MHz, +8.5 ppm). For ^1H NMR analysis, an aliquot (150 μL) of the solution was transferred to a sealed NMR tube and evaporated under argon, leaving a white chalky residue on the walls of the tube. $CDCl_3$ (700 μL) was then added and used as such for NMR analysis.

Preparation of 2,2-Dimethylnonan-3-one. To a clean, dry, 100-mL two-necked round-bottomed flask equipped with a stir bar was added magnesium turnings (3.504 g, 120 mmol) and a crystal of iodine. A condenser and addition funnel (50 mL) were attached and the iodine was sublimed onto the turnings with a heat gun. Once the flask had cooled, dry THF (30 mL) was added to the flask. In a separate 50-mL round-bottomed flask, a solution of 1-bromohexane (4.21 mL, 30 mmol) in dry THF (30 mL) was prepared and then added to the addition funnel. A small amount (~5 mL) of the halide solution was added to the THF over the magnesium. Once the reaction had begun, the rest of the solution was added dropwise from the addition funnel over the course of 30 min. Once addition was complete, the solution was refluxed for 2 h. The Grignard solution was then cooled over an ice bath and pivalaldehyde (1.09 mL, 10 mmol) was added dropwise. After the solution was stirred for 15 min, the ice bath was removed and the solution was stirred an additional 2 h. The reaction mixture was quenched with water, and then decanted into a separatory funnel containing pentane (30 mL), leaving the unreacted magnesium. The organic layer was washed with 1 M HCl (3 × 20 mL), 1 M NaOH (2 × 20 mL), and then D.I. water (1 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield the intermediate alcohol 2,2-dimethylnonan-3-ol as a colorless oil (1.502 g, 8.7 mmol, 87%). A 1.10 g sample of the alcohol (6.4 mmol) was transferred to a 50-mL round-bottomed flask equipped with a stir bar. Glacial acetic acid was added to the flask (4.27 mL, 6.4 mmol) then an addition funnel was connected to the top of the flask. Bleach (14.3 mL of a 5% solution, 9.6 mmol) was added to the top of the addition and allowed to slowly drip into the acid with stirring at a rate of approximately 1 drop per 5 s. The solution was stirred for 1 h following the complete addition of the bleach solution. Starch-iodide paper was used to confirmed the presence of excess hypochlorite, which was subsequently quenched by adding an excess of a saturated sodium bisulfite solution. The destruction of the hypochlorite is confirmed by starch-iodide test strips, then the solution is extracted with pentantes (3 × 15 mL). The combined organic layers are washed with 1 M NaOH (2 × 10 mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to obtain the product ketone as a colorless oil (1.09 g, 6.3 mmol, 97%).

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Supporting Information Available: Spectra for alkynyl and transition state analogue substrates along with computational parameters. This material is available free of charge via the Internet at http://pubs.acs.org.