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Catalytic Diastereoselective Reduction of α,β-Epoxy and α,β-Aziridinyl Ynones

Valérie Druais, Christophe Meyer,* and Janine Cossy*

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

christophe.meyer@espci.fr; janine.cossy@espci.fr

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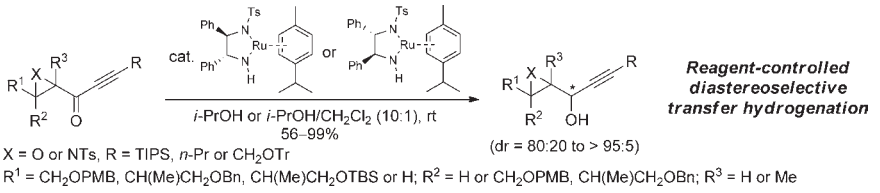
ABSTRACT



The Noyori transfer hydrogenation of α,β-epoxy and α,β-aziridinyl ynones leads to the corresponding α,β-epoxy or α,β-aziridinyl propargylic alcohols with high reagent-controlled diastereoselectivity.

The catalytic asymmetric synthesis of chiral secondary propargylic alcohols is an important research area due to the highly versatile utility of these building blocks and their extensive use as key intermediates in numerous total syntheses of bioactive natural products.[1] To achieve this goal, catalytic asymmetric alkynylation of aldehydes[2] and reduction of ynones[3,4] can be employed as complementary methods. Among the latter class of transformations, the Noyori transfer hydrogenation of ynones, catalyzed by (η^6-arene)ruthenium(II) complexes comprising a mono-*N*-tosylated diamine as a chiral ligand, constitutes a powerful method to synthesize propargylic alcohols with high enantiomeric purity.[4] It is also worth noting that a high level of reagent-controlled diastereoselectivity has been observed in the reduction of ynones possessing a stereocenter at the α or β position of the carbonyl group, including cases where the latter is substituted by a heteroatom.[5]

Herein, we report that the Noyori transfer hydrogenation of ynones bearing stereocenters substituted by an oxygen atom at both the α and β positions can be problematic and induce a strong substrate/reagent mismatch pairing. By contrast, high levels of reagent-controlled diastereoselectivities can be observed in the case of α,β-epoxy or α,β-aziridinyl acetylenic ketones.

At the outset of our studies was the assumption that optically active 1,2,3-triols of type **A**, possessing one

(1) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim, 1995.

(2) For a recent review, see: Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983.

(3) (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939. (b) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214–3217.

(4) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

(5) For examples with ynones bearing a stereocenter at the β position, see: (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667–3670. (b) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733–736. (c) Shin, Y.; Fournier, J.-H.; Fukui, Y.; Brückner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4634–4637. (d) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 17111–17117. (e) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666–3667. (f) Fukui, Y.; Brückner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, *8*, 301–304. (g) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2007**, *9*, 2461–2464. (h) Mandel, A. L.; Bellosta, V.; Curran, D. P.; Cossy, J. *Org. Lett.* **2009**, *11*, 3282–3285. For ynones bearing a stereocenter at the α position, see ref 4 and (i) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197–3199. (j) Marshall, J. A.; Ellis, K. *Tetrahedron Lett.* **2004**, *45*, 1351–1353. (k) Cantagrel, G.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2983–2986. (l) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2008**, *10*, 4489–4492. (m) Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1031–1035.

(6) Representative examples include aspicilin; see: (a) Hesse, O. *J. Prakt. Chem.* **1900**, *62*, 430–480. (b) Huneck, S.; Schreiber, K.; Steglich, W. *Tetrahedron* **1973**, *29*, 3687–3693. For erythromycin A, see: (c) Pal, S. *Tetrahedron* **2006**, *62*, 3171–3200. For triyne carbonate L-660,631, see: (d) Lewis, M. D.; Menes, R. *Tetrahedron Lett.* **1987**, *28*, 5129–5132. (e) Wright, J. J.; Puar, M. S.; Pramanik, B.; Fishman, A. *J. Chem. Soc., Chem. Commun.* **1988**, 413–414. (f) Lewis, M. D.; Duffy, J. P.; Heck, J. V.; Menes, R. *Tetrahedron Lett.* **1988**, *29*, 2279–2282. (g) Yadav, J. S.; Rajagopal, D. *Tetrahedron Lett.* **1990**, *31*, 5077–5080. For penarolide sulfate A_1, see: (h) Nakao, Y.; Maki, T.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *Tetrahedron* **2000**, *56*, 8977–8987. (i) Mohapatra, D. K.; Bhattasali, D.; Gurjar, M. K.; Khan, M. I.; Shashidhara, K. S. *Eur. J. Org. Chem.* **2008**, 6213–6224.

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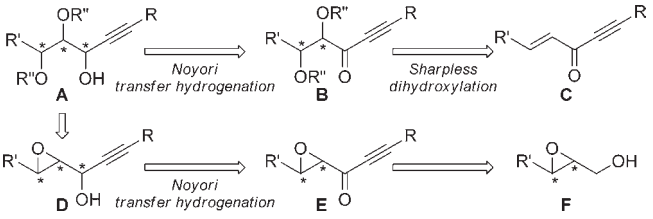
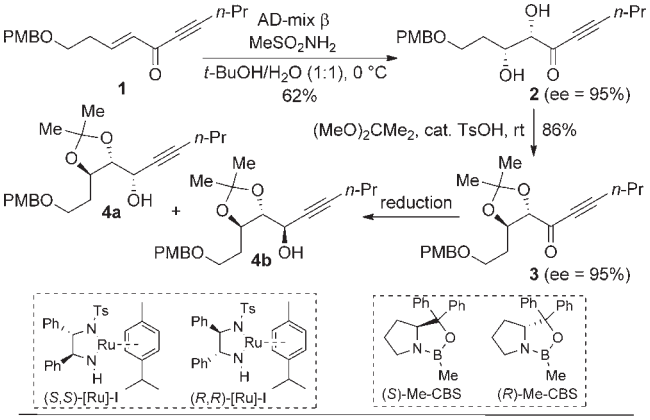
propargylic alcohol, should be valuable building blocks for the synthesis of trihydroxylated arrays (or their derivatives) which are encountered in many natural products.[6] With the aim of developing an efficient catalytic asymmetric route toward 1,2,3-triols **A**, it was envisaged to achieve the Noyori transfer hydrogenation of α,β-dihydroxy ynones **B** (or protected derivatives) which would be obtained by an enantioselective Sharpless dihydroxylation applied to enynones **C**. Alternatively, 1,2,3-triols **A** could be synthesized by ring opening with an oxygen nucleophile of α,β-epoxy propargylic alcohols **D**[7,8] which would arise from the Noyori transfer hydrogenation of α,β-epoxy ynones **E**. The latter compounds would be readily accessible from α,β-epoxy alcohols **F**. To our knowledge, ynones **B** or **E** had never been involved as substrates in Noyori transfer hydrogenation (Scheme 1).

Scheme 1. Catalytic Asymmetric Route toward 1,2,3-Triols **A**



Enynone **1** was selected as the test substrate[9] and subjected to a Sharpless enantioselective dihydroxylation using AD-mix β to afford the corresponding enantioenriched α,β-dihydroxy ketone **2** (62%, ee = 95%).[10] Attempts to achieve the Noyori reduction of the nonprotected α,β-dihydroxy ynone **2**, catalyzed by either (*R*,*R*)- or (*S*,*S*)-[Ru]-**I** (5−10 mol %) (*i*-PrOH, rt), did not provide the expected diastereomeric 1,2,3-triols. Instead, 5-*endo*-dig cyclization of the α hydroxyl group to the alkyne took place as the major competing pathway.[11] Unfortunately, neither the bis-TBS ether nor the bis-acetate derived from 1,2-diol **2** could be reduced under the same conditions even by using a high catalyst loading (up to 15 mol %). However ynone **3**, synthesized by protection of the 1,2-diol **2** as an acetonide (cat. TsOH, $Me_2C(OMe)_2$, rt, 86%), underwent successful Noyori transfer hydrogenation in the presence of (*R*,*R*)-[Ru]-**I** (10 mol %) [*i*-PrOH/CH_2Cl_2 (10:1), 0.5 h, rt] and afforded a 92:8 diastereomeric mixture of propargylic alcohols **4a** and **4b** which was isolated in 73% yield. By contrast, reduction of ynone **3** catalyzed by the enantiomeric complex (*S*,*S*)-[Ru]-**I** (10 mol %) [*i*-PrOH/CH_2Cl_2 (10:1)] was slightly slower (2 h, rt) and led to a 52:48 mixture of propargylic alcohols **4a** and **4b** which points out a strong substrate/reagent mismatch pairing.[12] For comparison, reduction of ynone **3** was carried out with $BH_3 \cdot SMe_2$ in the presence of the oxazaborolidine (*R*)-Me-CBS (THF, −30 °C) and a diastereomeric mixture of propargylic alcohols **4a** and **4b** was obtained with high diastereoselectivity (**4a**/**4b** = 95:5; 84%).[3b] In the presence of oxazaborolidine (*S*)-Me-CBS, the diastereoselectivity was much lower (**4a**/**4b** = 33:67; 86%) and controlled by the reagent only to a moderate extent.[13] Reduction of ynone **3** under Luche's conditions[14] led to a 73:27 mixture of the epimeric alcohols **4a** and **4b** (88%) as a result of a rather modest Felkin−Anh control[15] exerted by the stereocenter at the α position of the carbonyl group (Scheme 2).[12]

Scheme 2. Reduction of Ynone **3**



catalyst or reagents	conditions	4a/4b	yield
(*R*,*R*)-[Ru]-**I** (10 mol %)	*i*-PrOH/CH_2Cl_2 (10:1), rt, 0.5 h	92:8	73%
(*S*,*S*)-[Ru]-**I** (10 mol %)	*i*-PrOH/CH_2Cl_2 (10:1), rt, 2 h	52:48	65%
(*R*)-Me-CBS (2 equiv), $BH_3.SMe_2$	THF, −30 °C, 2 h	95:5	84%
(*S*)-Me-CBS (2 equiv), $BH_3.SMe_2$	THF, −30 °C, 2.5 h	33:67	86%
$NaBH_4$, $CeCl_3.7H_2O$	MeOH, −78 °C, 0.5 h	73:27	88%

The Noyori transfer hydrogenation of ketones is known to occur by a metal−ligand bifunctional catalysis from an 18-electron ruthenium hydride complex intermediate. A simultaneous transfer of the hydride and the protic N−H (axial) occurs to the carbonyl group, and a stabilizing arene C−H/π interaction with the alkyne is responsible for the high face selectivity observed in the reduction of ynones.[16] In the case of catalyst (*R*,*R*)-[Ru]-**I**, a match pairing is observed with ynone **3** since reduction can proceed through a Felkin−Anh transition state **TSa**.

(7) For a review on the ring opening of α,β-epoxy alcohols, see: Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 65–79.

(8) For the synthesis of 1,2,3-triols from α,β-epoxy alcohols, see: (a) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083–5093. (b) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636–1648. (c) For a recent contribution, see: Mukerjee, P.; Abid, M.; Schroeder, F. C. *Org. Lett.* **2010**, *12*, 3986–3989.

(9) For the preparation of the substrates, see Suppporting Information.

(10) Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Chem. Commun.* **2007**, 2494–2496.

(11) This transformation has been previously reported in the presence of mercuric salts; see ref 10.

(12) Diastereomeric ratios were determined in all cases by analysis of the crude product by ^1H NMR spectroscopy.

(13) Strong match/mismatch pairing has been previously noted during the CBS reduction of an ynone possessing an adjacent acetonide derived from an *anti-1,2*-diol; see: RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128–7135.

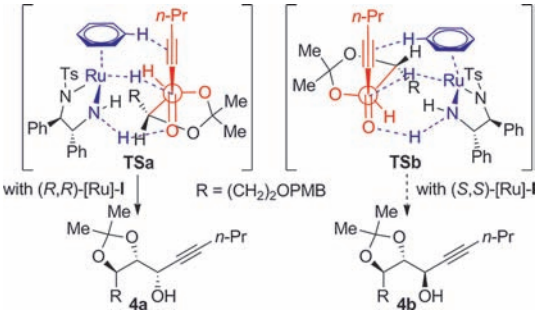
(14) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(15) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1224.

(16) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818–2821.

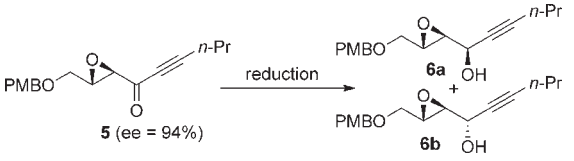
Conversely, the normal face selectivity of the catalyst generated from (*S*,*S*)-[Ru]-**I** would impose hydride delivery through a disfavored anti-Felkin–Anh transition state **TSb** (Scheme 3).

Scheme 3. Transition States for Reagent-Controlled Transfer Hydrogenation of Ynone **3**



Since protection of the 1,2-diol as an isopropylidene acetal in ynone **3** may be responsible for the difficulty in achieving high reagent-controlled diastereoselective Noyori reduction in the mismatched manifold, we investigated the reactivity of the less sterically demanding α,*β*-epoxy acetylenic ketones **E**. The readily available α,*β*-epoxy ynone **5** (ee = 94%)[9] was subjected to transfer hydrogenation using catalysts (*S*,*S*)- and (*R*,*R*)-[Ru]-**I** (*i*-PrOH, rt). Under these conditions, a diastereomeric mixture of propargylic alcohols **6a** and **6b** was obtained in each case with rather moderate but reagent-controlled diastereoselectivity (**6a**/**6b** = 75:25 and **6a**/**6b** = 13:87, respectively). It is well-known that α,*β*-epoxy ketones can be reduced to *anti*-α,*β*-epoxy alcohols under conditions that favor Cram-chelate control but access to *syn*-α,*β*-epoxy alcohols is more difficult.[17] Reduction of ynone **5** by $NaBH_4$ in the presence of $CaCl_2$ (MeOH, 0 °C) was found to proceed with a modest level of diastereocontrol (**6a**/**6b** = 30:70; 86%) presumably due to the low steric hindrance of the acetylenic chain (Scheme 4). Thus, the development of highly diastereoselective reagent-controlled reduction of α,*β*-epoxy ynones would be particulaly interesting.

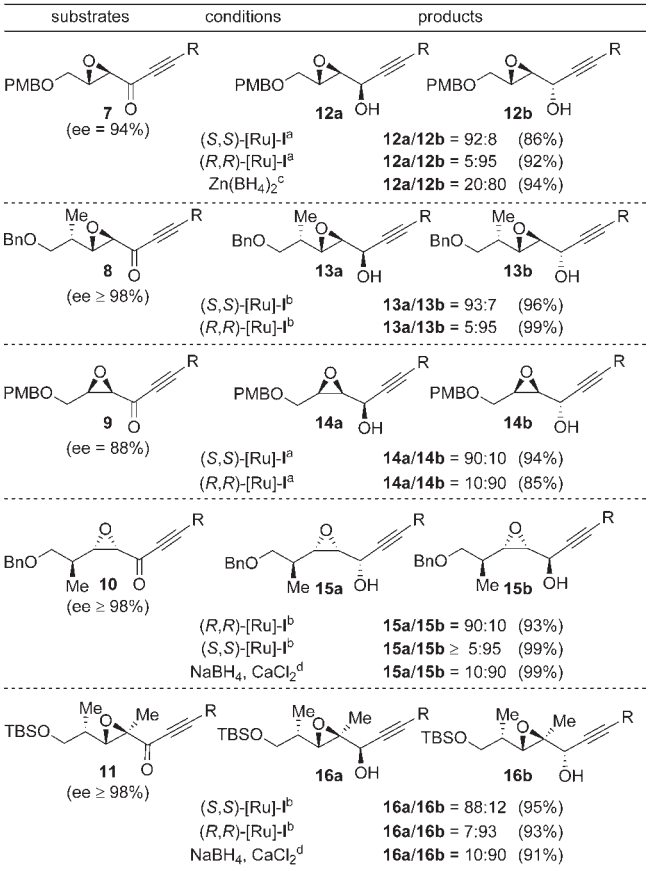
Scheme 4. Reduction of α,*β*-Epoxy Ynone **5**



catalyst / reagent	conditions	**6a**/**6b**	yield
(*S*,*S*)-[Ru]-**I** (5 mol %)	*i*-PrOH, rt, 2 h	75:25	80%
(*R*,*R*)-[Ru]-**I** (2 x 5 mol %)	*i*-PrOH, rt, 2 x 12 h	13:87	84%
$NaBH_4$, $CaCl_2$	MeOH, 0 °C, 0.25 h	30:70	86%

As silylated acetylenic ketones are excellent substrates in Noyori enantioselective reductions,[4] the reactivity of several (triisopropylsilylethynyl) α,*β*-epoxy ketones **7**–**11** was investigated.[9] The latter ynones were thus subjected to transfer hydrogenation catalyzed by either (*S*,*S*)- or (*R*,*R*)-[Ru]-**I** (5 mol %) in *i*-PrOH or *i*-PrOH/CH_2Cl_2 (10:1) (Table 1).[18]

Table 1. Noyori Transfer Hydrogenation of (Triisopropylsilylethynyl) α,*β*-Epoxy Ketones (R = TIPS)



[a] Catalyst (5 mol %), *i*-PrOH, rt, 1.5 h. [b] Catalyst (5 mol %), *i*-PrOH/CH_2Cl_2 (10:1), rt, 1.5 h. [c] Et_2O, 0 °C. [d] MeOH, 0 °C.

Reactions occurred smoothly (rt, 1.5 h), and the corresponding *syn*- or *anti*-α,*β*-epoxy propargylic alcohols **12a**–**16a** or **12b**–**16b**, respectively, were obtained with uniformely high reagent-controlled diastereoselectivities (dr ≥88:12) whether the oxirane is *trans*-α,*β*-disubstituted (substrates **7** and **8**) or *cis*-α,*β*-disubstituted (substrates **9** and **10**), irrespective of the nature of the substituent (linear or branched) at the *β* carbon, or α,α,*β*-trisubstituted (ynone **11**) (Table 1).[12,19] The high reagent-controlled

(17) (a) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1995**, *51*, 679–686. (b) Li, K.; Hamann, L. G.; Koreeda, M. *Tetrahedron Lett.* **1992**, *33*, 6569–6570. (c) Fujii, H.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1992**, 967–970. (d) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723–4726. (e) For a review on α,*β*-epoxy ketones, see: Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359–2383.

(18) The catalyst can be added as a solid or as a solution in CH_2Cl_2.

(19) To confirm the stereochemical outcome, reduction of representative ynones **7**, **10**, and **11** was also achieved with achiral reagents such as $Zn(BH_4)_2$[17c] or $NaBH_4/CaCl_2$[17a] to afford the *anti*-α,*β*-epoxy alcohols (**12b**, **15b**, and **16b**) as the major diastereomers.

diastereoselectivity observed in the Noyori transfer hydrogenation of α,β-epoxy acetylenic ketones is noteworthy since reduction of such substrates using $BH_3 \cdot SMe_2$ in the presence of (*R*)- or (*S*)-Me-CBS reagent can lead to a strong substrate/reagent mismatch pairing.[20]

Due to the high levels of diastereoselectivity observed for the Noyori transfer hydrogenation of α,β-epoxy ynones, it was envisaged to examine the reactivity of several structurally related *N*-tosyl-α,β-aziridinyl ynones **17**–**19** and **20**, readily prepared from L-serine or L-threonine, respectively (Table 2).[9]

For ynones **17**–**19** possessing a monosubstituted aziridine, diastereoselective reagent-controlled Noyori reduction could be achieved whatever the substituent on the alkyne (R = *n*-Pr, CH_2OTr, or TIPS); however the use of catalyst (*S*,*S*)-[Ru]-**I** generally led to slower reactions requiring a higher catalyst loading to reach completion. Ynone **20** possessing a *cis*-α,β-disubstituted aziridine also underwent reagent-controlled transfer hydrogenation, and it is worth noting that the diastereoselectivity was high only in the presence of catalyst (*S*,*S*)-[Ru]-**I** (Table 2).[21]

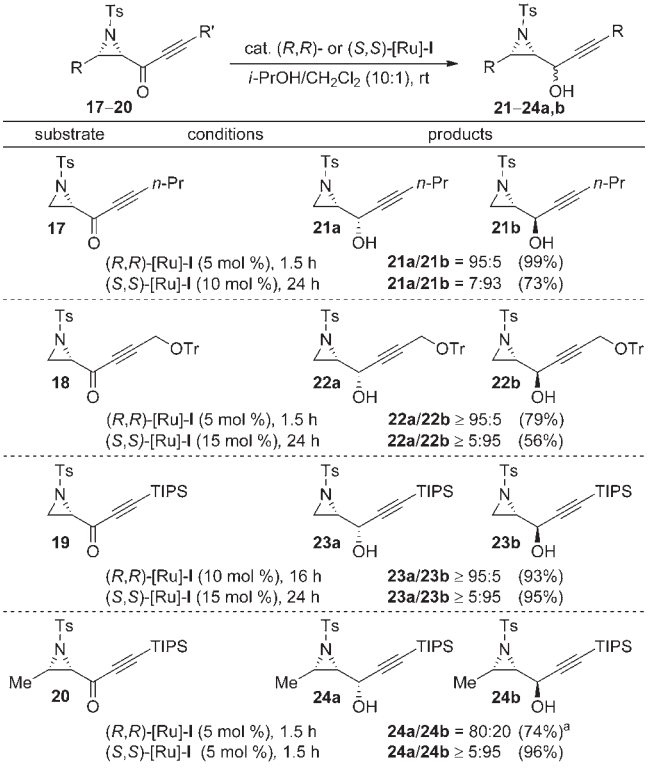
In conclusion, we have reported that the Noyori transfer hydrogenation of α,β-epoxy ynones, contrary to other α,β-dialkoxy ynones, as well as α,β-aziridinyl ynones can proceed with a high level of reagent-controlled diastereoselectivity to deliver α,β-epoxy or α,β-aziridinyl propargylic alcohols that constitute highly functionalized useful building blocks for the synthesis of natural products.

Acknowledgment. V.D. thanks the MRES for a grant.

(20) Li, J.; Park, S.; Miller, R. L.; Lee, D. *Org. Lett.* **2009**, *11*, 571–574.

(21) Reduction of 1-(1-phenylethyl)aziridines-2-acylaziridines can proceed with a high level of Felkin-Anh (L-selectride) or Cram-chelate ($NaBH_4/ZnCl_2$) diastereocontrol; see: (a) Yun, J. M.; Sim, H. S.; Lee, W. K.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 7675–7680. (b) Singh, A.; Kim, B.; Lee, W. K.; Ha, H.-J. *Org. Biomol. Chem.* **2011**, *9*, 1372–1380.

Table 2. Noyori Transfer Hydrogenation of α,β-Aziridinyl Ynones



[a] Isolated yield of the major pure diastereomer.

Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.