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J. Am. Chem. Soc., **2003**, 125 (41), 12422-12423• DOI: 10.1021/ja035467z • Publication Date (Web): 23 September 2003

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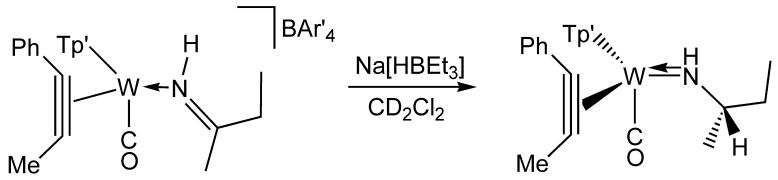

80:20 *E/Z*
2a

94:6 diastereomer ratio
1a (*SS* + *RR*)

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Published on Web 09/23/2003

Methyl/Ethyl Differentiation in Diastereoselective Hydride Addition to [Tp′W(CO)(PhCCMe)(NH═CMeEt)][BAr′$_4$]

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The importance of chiral amines to organic synthesis and to the pharmaceutical industry accounts for the development of multiple methods for stereoselectively converting imines to amines.[1] Stereoselective synthetic routes to amine products include asymmetric hydrogenation,[2] hydrosilylation,[3] and the Strecker synthesis.[4] Stereoselective nucleophilic addition to imines has been accomplished by using N-bound chiral substituents[5] or chiral ligands.[6] These routes generally lead to secondary amines, some of which can be converted to primary amines.

In most examples of stereoselective reduction of an unsaturated bond, one reagent isomer (*E*/*Z*) predominates, and reduction occurs primarily from one direction to give high stereoselectivity. There are few examples where the *E*/*Z* ratio has no impact on the stereoselectivity of the reaction.[7] To favor one isomer of the substrate, hydrogen and aryl substituents are often employed; discrimination between methyl and ethyl groups in any reaction is rare.[8]

Stoichiometric diastereoselective additions to imines are also possible in coordinated imine complexes with high *E*/*Z* ratios. Addition of MeLi to the imine in a 95:5 *E*/*Z* mixture of [Cp(PPh$_3$)(NO)Re(N(Me)═CHPh)][OTf] gives Cp(PPh$_3$)(NO)Re(N(Me)-CHMePh) with a 74:26 diastereomer ratio.[9] Restriction of *E*/*Z* isomers by *o*-metalation in [(η^6-C$_6$Me$_6$)(PMe$_3$)Ru(N(Ph)═CHPh)][BF$_4$] gives a 98:2 diastereomer ratio of amido products upon addition of MeLi.[10] Cyanide addition to the *E* isomer of [Tp′W(CO)(PhCCMe)(NH═CHMe)][BF$_4$] occurs with high diastereoselectivity.[11]

Reported here is hydride addition to an *E*/*Z* mixture of the coordinated imine in [Tp′W(CO)(PhCCMe)(NH═CMeEt)][BAr′$_4$] (**2a**) (Tp′ = hydridotris(3,5-dimethylpyrazolyl)borate, BAr′$_4$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) to form an amido complex with high diastereoselectivity through *E*/*Z* imine isomer reactivity differences. This system effectively differentiates between methyl and ethyl groups at the prochiral carbon.

Amido complexes, Tp′W(CO)(PhCCMe)(NHCHRR′) (**1a**−**c**; R/R′ = Me/Et, **1a**; Me/Me, **1b**; Et/Et, **1c**), were synthesized according to the literature procedures for **1a**.[12] Complex **1a** is synthesized in a 1:1 diastereomer ratio. Oxidation of these amido complexes was shown to give imine complexes, [Tp′W(CO)(PhCCMe)(NH═CRR′)][BAr′$_4$] (**2a**−**c**).[12] Complex **2a** exists as a 75:25 ratio of *E* and *Z* isomers that were assigned by NOESY.[13] Recrystallization of **2a** from CH$_2$Cl$_2$/THF/hexanes[14] provided a nonequilibrium ratio of *E*/*Z* imine isomers ranging from 80:20 to 93:7. The corresponding azavinylidene complexes **3a**−**c** were prepared by deprotonation of imine complexes **2a**−**c** with KH in THF.[12]

An NMR sample in CD$_2$Cl$_2$ of 90:10 *E*/*Z* imine complex **2a** was isomerized to a 75:25 *E*/*Z* ratio immediately upon addition of 5 mol % NEt$_3$. Isomerization of the imine can occur by deprotonation to form azavinylidene complex **3a** followed by reprotonation of the opposite nitrogen face. Isomerization of imine complex **2a** was also observed in THF-d_8 in the absence of base, precluding the use of THF as solvent for the hydride addition reactions.

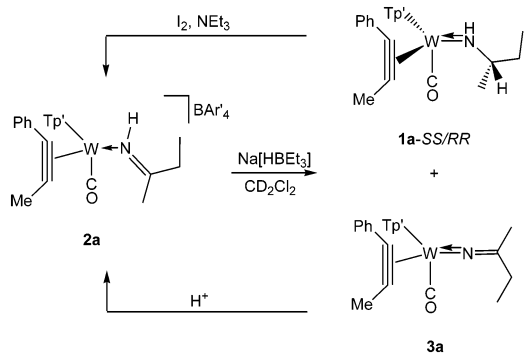


Figure 1. Amido complex **1a** is formed with a diastereomer ratio higher than the *E*/*Z* ratio of the starting imine complex.

Table 1. Product Distribution for Hydride Addition Reactions to **2a**

imine *E*/*Z* ratio	amido		azavinylidene
	major diastereomer	minor diastereomer	
80:20	70	5	25
93:7	78	3	18

In an NMR tube, Na[HBEt$_3$] was added to a CD$_2$Cl$_2$ solution of an 80:20 mixture of *E*/*Z* imine isomers of complex **2a**. The expected product, amido complex **1a**, was observed by NMR spectroscopy, but a surprising 94:6 diastereomer ratio (*SS*/*RR*:*RS*/*SR*)[15] was evident (Figure 1). This ratio is unusually high considering the low 80:20 *E*/*Z* ratio of the coordinated imine reagent. Deprotonation of imine complex **2a** to give azavinylidene complex **3a** was also evident.

In a second experiment, Na[HBEt$_3$] was added to a solution of a 93:7 *E*/*Z* isomer mixture of imine complex **2a** in an NMR tube. Slightly higher diastereoselectivity was observed, 96:4, and there was less deprotonation. Diastereoselectivities and ratios of addition to deprotonation are shown in Table 1.

The results of the hydride addition reactions suggest that the *E* isomer preferentially adds hydride because more *E* isomer in the starting material increases the yield of amido product. Having more *Z* isomer in the starting material promotes deprotonation.

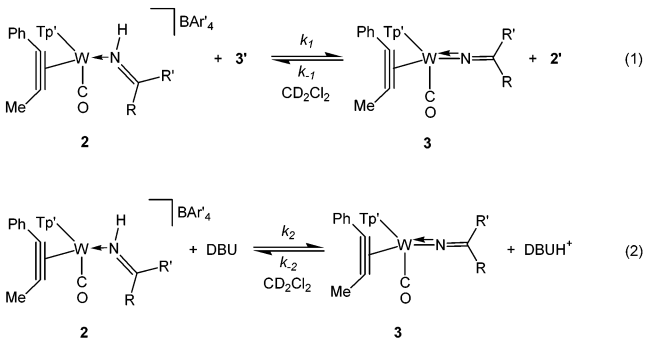
Given that both hydride addition and imine deprotonation[16] were occurring, the relative kinetic acidity of the imine complexes is likely to be mechanistically important. Because of the fast isomerization of **2a** in the presence of base, it is difficult to separate the reactivity of the *E* and *Z* isomers. To probe the reactivity differences of the *E* and *Z* isomers, we looked at the symmetrically substituted imine complexes **2b** (Me/Me) and **2c** (Et/Et) as models. The proton exchange rates between imine complexes and azavinylidene complexes (**2b**/**3b** and **2c**/**3c**) were measured by ^{1}H NMR line shape analysis (eq 1).[17] The rate of exchange with DBU (1,8-diazabicyclo-

10.1021/ja035467z CCC: $25.00 © 2003 American Chemical Society

Table 2. Proton Transfer Rate Constants for Eqs 1 and 2 in M^{-1} s^{-1}

R/R′	k_1 (k_{-1})	k_2	k_{-2}
Me/Me (**2b**)	4600 ± 2000	$(39 \pm 10) \times 10^4$	$(20 \pm 4) \times 10^4$
Et/Et (**2c**)	470 ± 300	$(1.8 \pm 0.2) \times 10^4$	$(0.61 \pm 0.1) \times 10^4$

[5.4.0]undec-7-ene) as a base was measured by line shape analysis as well (eq 2). The self-exchange rate does not contribute significantly to the overall rate of the reaction in eq 2, so k_1 was ignored in the calculation of k_2 and k_{-2}. Rate constants for eq 1 and 2 are shown in Table 2.



The difference in the rate constants for imine complexes **2b** and **2c** can be explained by the bulk of the imine substituents. Complex **2b**, with a methyl group cis to the imine proton, undergoes rapid proton transfer to DBU. When an ethyl group is placed cis to the imine proton as in complex **3b**, the rate of proton transfer from the imine ligand decreases by a factor of 20.

Transferring this argument to imine complex **2a** provides a plausible explanation for the reactivity differences between the *E* and *Z* isomers. The *Z* isomer has a methyl group cis to the imine proton and would be expected to be rapidly deprotonated by hydride. The *E* isomer has an ethyl group cis to the imine proton, so it undergoes slower deprotonation allowing for hydride addition to dominate.

Addition of hydride to imine complex **2b** leads to an 80:20 ratio of addition to deprotonation. Imine complex **2c** reacts with hydride to give a 30:70 ratio of addition to deprotonation. Changing the imine substituents not only affects the barrier to deprotonation but also the barrier for hydride addition to the imine carbon. While only qualitative, reaction of hydride with **2c** is noticeably slower than that with **2b**. All of these reactions occur in a matter of seconds.

Hydride addition to *N*-protio imine complex **2a** has been shown to occur with high diastereoselectivity to form a primary amido complex (**1a**). This result is attributed to a difference in the kinetic acidity of the *E* and *Z* imine isomers. Most of the *E* isomer undergoes hydride addition to give amido complex **1a**, while most of the *Z* isomer is deprotonated to form azavinylidene complex **3a**. This difference in reactivity leads to effective differentiation between methyl and ethyl groups and accounts for the high diastereoselectivity observed for hydride addition despite the *E*/*Z* isomer mixture in the reagent imine complex.

Acknowledgment. We gratefully acknowledge the Petroleum Research Fund (38554-AC3) for their support.

Supporting Information Available: NOE data, X-ray data, and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Assignment of the *E*/*Z* isomers has been corrected from ref 12 using NOESY.
(14) Recrystallization by slow diffusion of hexanes into a solution of **2a** in 3:2:1 hexanes:CH_2Cl_2:THF gives a nonequilibrium *E*/*Z* ratio of imine complex isomers.
(15) Absolute assignment of the diastereomers was obtained by X-ray diffraction of [Tp′W(CO)(PhCCMe)(NH_2CHMeEt)][BAr′$_4$] (**4a**).
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JA035467Z