ASYMMETRIC VARIANTS OF THE HENRY REACTION

Reported by Jeremy Wilmot October 10, 2005

INTRODUCTION

The Henry reaction, the coupling of a nitroalkane nucleophile with a carbonyl electrophile, is a widely used transformation with a long history, dating back to its discovery in 1895.[1] The resulting β-nitroalcohol can be easily transformed into other useful functionality through oxidation, reduction, elimination, etc., depending on the requirements of the synthesis to which it is applied. With the potential generation of two stereogenic centers in a *syn* or *anti* configuration, this reaction is ideal for the introduction of chiral information. Surprisingly, although it is conceptually similar to the powerful aldol coupling reaction, an asymmetric variant of the Henry reaction has only recently been reported by Shibasaki and co-workers, in 1992.[2] Since then, interest in this subject has expanded greatly, with many groups developing and optimizing new catalytic methods. Shibasaki's work with rare-earth heterobimetallic-catalyzed Henry reactions was followed by systems using dinuclear Zn complexes (Trost),[3] Cu and Zn complexes of bis(oxazoline) and bisthiazoline (Jørgensen, Xu),[4,5] and fluoride-catalyzed couplings using silyl nitronates (Jørgensen, Maruoka).[6] This report details the various catalyst systems, noting their advantages and limitations, and also provides some examples of their use in total synthesis.

Rare-Earth Heterobimetallic Catalysts

In 1992, Shibasaki and co-workers reported the first catalytic asymmetric version of the Henry reaction by using heterobimetallic catalyst **1a,** prepared from $La_3(O\text{-}t\text{-}Bu)_9$, (S)-(-)-binaphthol, LiCl, and H_2O. The catalyst was shown to have the structure shown in Figure 1 by ^1H and ^{13}C NMR spectroscopy, as well as x-ray crystallography.[8] This catalyst afforded the (*R*)-β-nitroalcohol products **3** in 79-91% yield and 86:14-95:5 er from various aliphatic aldehydes and 10 equivalents of nitromethane.[2] The utility of this transformation was demonstrated by the concise synthesis of (*S*)-arbutamine (**4**) from aldehyde **2** and nitromethane to yield nitro-alcohol **3** in 93% yield and 96:4 er[8] (Scheme 1).

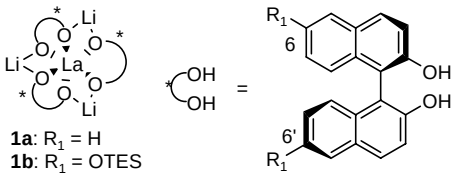
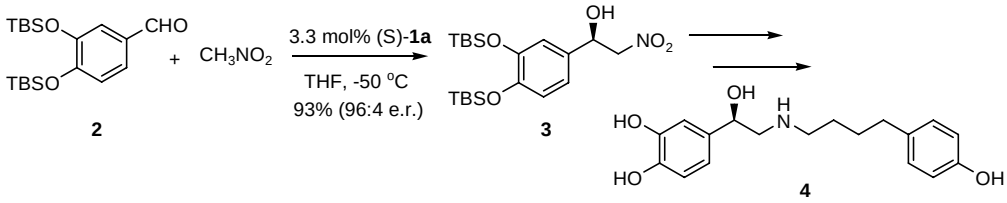


Figure 1. Structure of Shibasaki's Catalyst

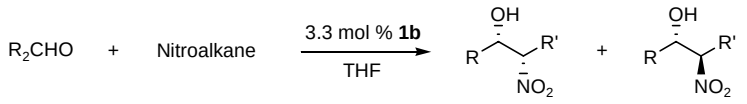
Scheme 1. Synthesis of (*S*)-Arbutamine.



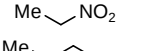
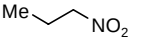
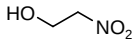
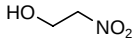
2 **3** **4**

The synthetic utility of the asymmetric Henry reaction was expanded through the use of prochiral nitroalkanes instead of nitromethane to generate two stereocenters, in which case the catalyst is required to control the enantioselectivity of the reaction as well as its diastereoselective outcome. Shibasaki applied his catalyst system to more complex nitro compounds to determine its effect on diastereoselectivity. The addition of triethylsiloxy groups to the 6 and 6' positions of the binaphthol ligands produced catalyst **1b** (Figure 1), which led to the generation of β-nitroalcohols with high diastereoselectivity. Products favored the *syn* isomer (7) with a dr as high as 93:7, while good yields (70-97%) and enantioselectivities (96:4-98:2 er) were maintained (Table 1).[9]

Table 1. Asymmetric Henry Reaction with Various Nitroalkanes.

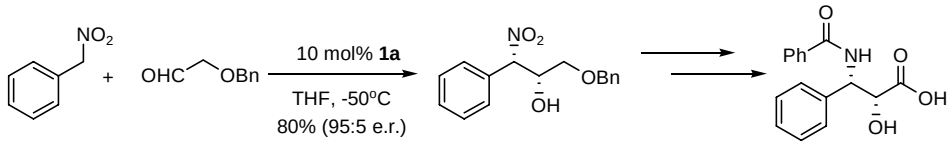


5 **6** **7** **8**

R_2	Nitroalkane	T (°C)	Time (h)	Yield (%)	*syn:anti*	er of *syn* (%)
$PhCH_2CH_2$		-20	75	70	89:11	96:4
$PhCH_2CH_2$		-40	138	85	93:7	98:2
$PhCH_2CH_2$		-40	111	97	92:8	98:2
$CH_3(CH_2)_4$		-40	93	96	92:8	98:2

Barua and co-workers used this technology in a concise synthesis of the C-13 side-chain of taxol (**12**). Phenylnitromethane (**9**) and aldehyde **10** were treated with catalyst **1a** to afford (2*R*, 3*S*) nitro-alcohol **11** in 80% yield and 95:5 er, although the diastereomeric ratio was not reported.[10] This intermediate was then elaborated to **12** in five steps and 33% yield from **11**.

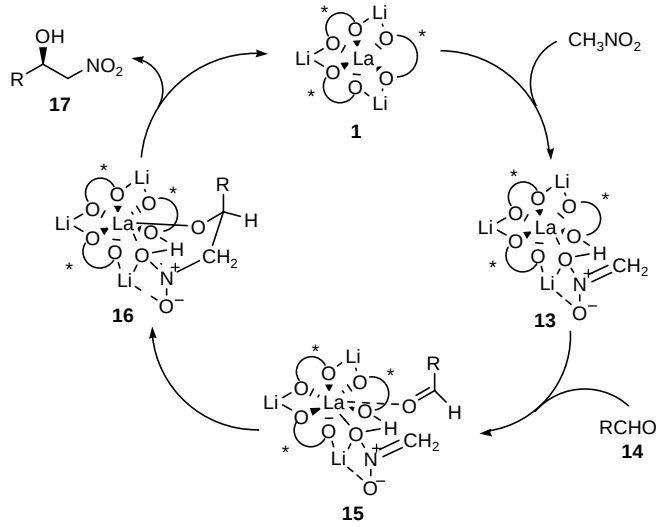
Scheme 2. Synthesis of the C-13 Side-chain of Taxol.



9 **10** **11** **12**

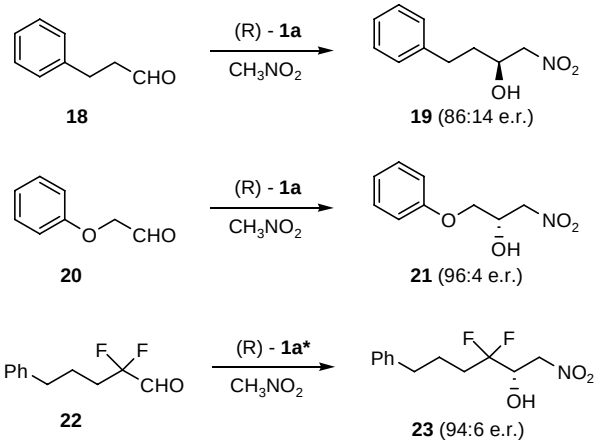
Shibasaki's rare-earth heterobimetallic catalyst plays a dual role in the catalytic cycle: it acts both as a Brönstead base to form the nitronate and as a Lewis acid to activate the electrophile. Therefore, both participants in the reaction are coordinated to the complex during the reaction, suggesting that the structure of both the nitronate and the electrophile should have an impact on the stereochemical outcome of the reaction (Scheme 3).[7] First, the binaphthoxide moiety deprotonates the nitroalkane to form nitronate complex **13**. Subsequent activation of the aldehyde (**14**) by the lanthanum complex provides complex **15**, which undergoes nucleophilic addition to form complex **16**. Subsequent release of the nitro-alcohol **17** regenerates the catalyst. These catalysts have been tuned to provide optimal

Scheme 3. Proposed Catalytic Cycle.



enantioselectivity for specific substrates. While catalyst **1** provided the best enantioselectivity for aliphatic aldehydes, europium complexes proved to be optimal for asymmetric Henry reactions of aromatic aldehydes.[11] A more profound substrate effect was detected with some aldehydes that contained α-heteroatoms, in which case enantiotopic facial selection was reversed. This reversal was seen in both α-oxo aldehydes and α,α-difluoro aldehydes (Scheme 4).[12,13] For example, when aldehyde **18** was subjected to the appropriate reaction conditions, nitroalcohol **19** was obtained, whereas when α-oxo aldehyde **20** was used, a complete reversal in facial selectivity was observed. A similar effect was observed when α,α-difluoro aldehyde **22** reacted with nitromethane to yield alcohol **23**. These effects could be due to hydrogen bonding between the α-heteroatom and the binol formed from the protonation of binaphthyl alkoxide during nitronate formation. Alternatively, the effect could result from Lewis acid/Lewis base interactions between the α-hetroatom and a lithium cation.

Scheme 4. Reversal of Enantioselectivity.



* - Sm complex provided the best enantioselectivity

Copper-Bis(oxazoline) Catalysts

Jørgensen and co-workers recently reported the use of Cu-bis(oxazoline) (BOX) complexes to catalyze asymmetric Henry reactions of nitromethane with α-keto esters.[14] The use of ketones is notable because it allows for the asymmetric preparation of chiral tertiary alcohols, a challenging task in synthetic organic chemistry. Screening of bis(oxazoline) ligands **24**, **25**, and **26**, and Lewis acids in the reaction of nitromethane with ethyl pyruvate (**27**), using triethylamine (TEA) as base, led to the finding that ligand **24** and $Cu(OTf)_2$ provided β-nitro-α-hydroxy ester **28** in 95% isolated yield with 96:4 er (Table 2, Scheme 5). It is interesting to note that use of $Zn(OTf)_2$ as the Lewis acid with this ligand resulted in

Scheme 5. Cu-BOX Ligands.

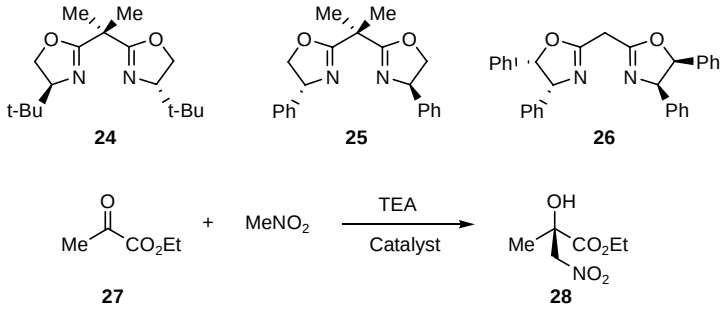
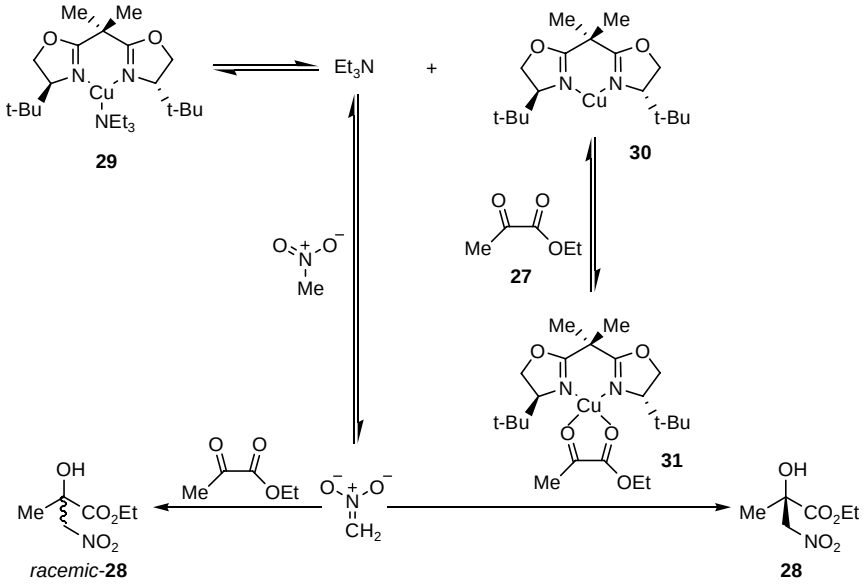


Table 2. Optimization of the catalytic enantioselective Henry reaction of 27 and nitromethane

Catalyst	Loading (%)	TEA (%)	Conversion (%)	e.r.
24-$Cu(OTf)_2$	20	20	>95	96:4
25-$Cu(OTf)_2$	20	20	>95	57:43
26-$Cu(OTf)_2$	20	20	11	59:41
24-$Cu(OTf)_2$	20	10	11	74:26
24-$Cu(OTf)_2$	20	40	>95	<52:48
----------	---	20	>95	---------
24-$Zn(OTf)_2$	20	20	87	42:58

reversal of enantiofacial selection, although the enantiomeric ratio was low. The bases N-methylmorpholine, $PhNMe_2$, Bn_3N, $Et(i\text{-}Pr_2)N$, pyridine, and K_2CO_3 were all screened, but resulted in lower yields than TEA. K_2CO_3 led to similar yields but much lower enantioselectivity. As shown in Table 2, the use of equimolar amounts of Brönsted base and catalyst plays a vital in this reaction. It was hypothesized that the reaction proceeds through the series of equilibria shown in Scheme 6. Excess base shifts the equilibrium to inactive complex **29**, allowing the reaction to proceed through the slower racemic route to yield racemic **28**. Excess catalyst (**30**) also shifts the equilibrium to complex **29**, which causes the reaction to stall.

Scheme 6. Proposed Catalytic Route for Cu-BOX Catlysts.



Evans and co-workers have reported a similar catalyst system in which no external base was necessary; however, aldehydes were used as the electrophiles instead of ketones.[15] Ligand **31** (Figure 2)**,** combined with $Cu(OAc)_2$, catalyzed the reaction of various aliphatic and aromatic aldehydes with 10 equivalents of nitromethane in good yields (66-95%) and high enantioselectivities (94:6-97:3 er). In these reactions, the acetate anion displaced from the metal center by nitromethane coordination is basic enough to deprotonate the nitroalkane. Xu and co-workers have also reported a modification of the bis(oxazoline)-Lews acid-catalyzed reaction utilizing tridentate ligand **32** (Figure 3). When the complex resulting from ligand **32** and $Cu(OAc)_2$ (20 mol%) was used in the reaction between ethyl pyruvate (**27**) and nitromethane, with TEA (20 mol%) as base, the (*S*) enantiomer of the β-nitro-α-hydroxy ester **28** was obtained in 61% yield

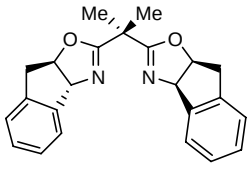


Figure 2. Ligand developed by Evans.

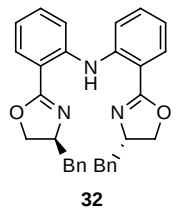
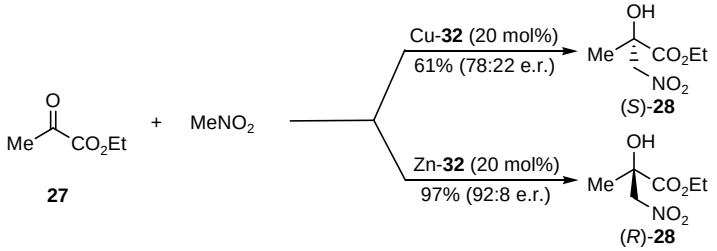


Figure 3. Ligand developed by Xu.

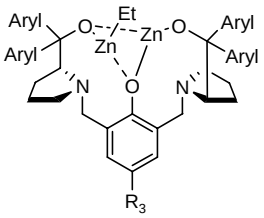
and 78:22 er.[15] However, 50 mol% Et_2Zn and 20 mol% ligand **32** at 0 °C for 24 hours provided (*R*)-**28** in 97% yield and 92:8 er (Scheme 7).[16] With improvements in the Cu^{2+} reaction, these modifications could provide a catalyst system in which both enantiomers of β-nitro-α-hydroxy esters might be available by simply changing the Lewis acid.

Scheme 7. Metal-Dependant Reversal of Enantioselectivity.



Dinuclear Zinc Catalysts

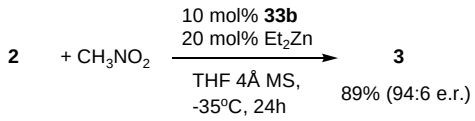
The scope of the catalytic asymmetric Henry reaction was further expanded when Trost applied dinuclear catalyst **33** (Figure 4) to the Henry reaction. This catalyst system was efficient for the conversion of α-branched aldehydes to the corresponding primary β-nitroalcohols, but the yields and enantioselectivities were generally lower with unbranched aldehydes.[17] Good selectivity could be obtained, however, with unbranched aldehydes by the use of lower temperatures and increased equivalents of nitromethane, although modification of the ligand in an attempt to improve selectivity met with limited success. Nevertheless, enantioselectivity in the reaction of nitromethane with aldehyde **2** to form nitroalkane **3**, a precursor in the synthesis of (-)-arbutamine (**4**) and (-)-denopamine (**34**), was increased when the aryl substituent on the ligand was changed from phenyl (**33a**) to the bulkier binaphthyl (**33b**) (Figure 4).

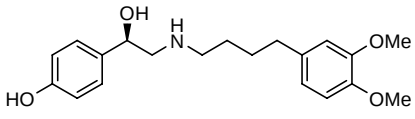


33a - Aryl = Ph
33b - Aryl = binaphthyl

Figure 4. Structure of Trost's dinuclear zinc catalyst.

Scheme 8. Synthesis of 3 using 33b.



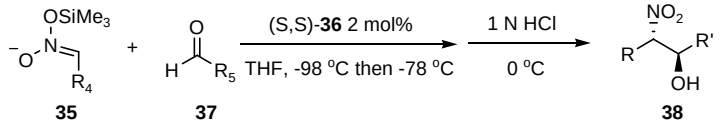


34

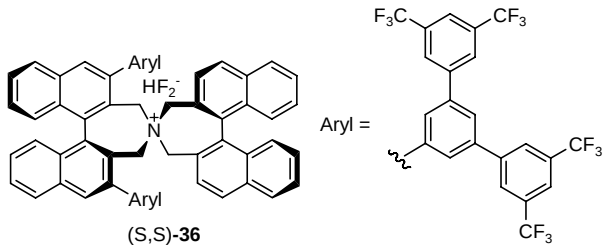
Silyl Nitronates

The fluoride-ion promoted Henry reaction of silyl nitronates has been known in the literature for some time.[19] An asymmetric version of this reaction was first reported by Jørgensen and co-workers in 2002 and used bisoxazoline ligands **24-26** (Scheme 5), with tetrabutylammonium triphenyldifluorosilicate (TBAT) as the fluoride source.[20] Unfortunately, the coupling of propyl- and

Scheme 9. Chiral Tertiary Ammonium Fluoride Catalyst.



R_4 = Me, Et, $BnO(CH_2)_2$ R_5 = Ph, *p*-Me-Ph, *p*-F-Ph, ß -Np



hexyl-silylnitronates with various aldehydes resulted in only moderate yields and enantioselectivities. Since the products were prone to undergo retro-Henry reactions, they were immediately converted to the corresponding Mosher esters. The diastereomeric ratio of the Mosher ester was then used to determine the enantiomeric ratio of the Henry reaction. It should be noted that the retro-Henry side reactions were not observed in using other catalyst systems. The stereoselectivity of the reaction was moderate, with the best result reported at 82:18 er and 5:1 dr, favoring the *anti* products. Maruoka and co-workers reported better results with the use of a catalytic chiral fluoride source.[21] Their approach was to treat the silyl nitronate (**35**) with the chiral quaternary ammonium fluoride compound **36** in the presence of an aromatic aldehyde (**37**) at low temperature for 4 hours. (Scheme 9) Trimethylsilyl nitronates were found to be the most favorable of the silyl nitronates examined. High yields (70-94%) favoring the *anti* isomer in greater than 85:25 dr and greater than 95:5 er of the (1*R*, 2*S*) enantiomer of **38** were obtained.

Summary and Conclusions

The available catalytic systems for the asymmetric Henry reaction all have different strengths and weaknesses. Shibasaki's heterobimetallic system can be used to obtain high optical purities as well as high diastereoselectivities, although the combination of low temperature and reaction time of at least 72 hours limits its practicality. The copper-bis(oxazoline) complexes can catalyze the reaction of nitromethane with keto-esters to produce chiral tertiary alcohols, but there has been no report of their use with prochiral nitroalkanes. Trost's dinuclear zinc complexes can produce high enantioselectivities and have been used in the synthesis of several molecules. The activation of silyl nitronates for the Henry reaction, using chiral tertiary ammonium fluoride catalysts, is very promising: the reactions are relatively fast, and substrates other than nitromethane can be used to produce products in very high diastereo and enantiomeric purity. The carbonyl substrate scope, however, is somewhat limited, with

only reactions of aryl aldehydes being reported. Preparation of the silyl nitronates adds another step as well.

The asymmetric Henry reaction is a useful source of enantiomerically enriched β-nitroalcohols. When starting with a ketone, a synthetically challenging chiral tertiary alcohol is obtained. Two stereocenters can be produced with good diastereoselectivity as well as high optical purity, and the nitro groups of the resulting compounds can be easily transformed into useful functional groups such as α-hydroxy acids, amino alcohols, and α-hydroxy ketones, among others. The development of a number of catalytic systems for the asymmetric Henry reaction, coupled with the functional versatility of the β-nitroalcohol products, significantly increases the synthetic utility of this transformation.

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