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Efficient synthesis of chiral phenethylamines: preparation, asymmetric hydrogenation, and mild deprotection of ene-trifluoroacetamides

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Abstract—A mild and efficient route to enantioenriched aryl alkyl amines from ketones has been developed. The first successful synthesis and asymmetric hydrogenation of ene-trifluoroamides from oximes gave highly enantioenriched trifluoroacetamides (94–98% ee). The corresponding phenethyl amides are liberated under mild conditions (K_2CO_3, MeOH/H_2O). In addition, a new application of Josiphos ligands toward the asymmetric hydrogenation of both ene-acetamides and ene-trifluoroacetamides was discovered.

Optically active amines are found in abundance within biologically active natural products and pharmaceutical agents.[1] They have also been established as a useful class of resolving agents for organic synthesis.[2] While numerous synthetic routes to enantioenriched amines have been developed, catalytic asymmetric hydrogenation of the corresponding enamides is arguably one of the most valuable methods due to the inherent efficiency of these atom-economical processes. Originally communicated by Kagan,[3] asymmetric hydrogenation of enamides allows for convenient arrival to enantioenriched acetamides that can be converted to the amines by removal of the acetate functionality. Since that initial discovery, the overwhelming focus of subsequent research in this area has been on the design of new chiral ligands for asymmetric hydrogenations. Consequently, many catalytic systems have been discovered that can reduce a variety of enamides in high yield and with very high enanantioselectivity.[4] While the field of enamide asymmetric hydrogenation has matured, there has not been a corresponding application of these methods to complex synthetic targets. The reason for this discrepancy may lie in the fact that little attention has been placed on the preparation and design of practical functionality for the enamide itself. With few exceptions,[5] enamides used in these processes are in the form of acetamides derived from oximes and acetic anhydride. These enamides suffer from a significant limitation: the products of the asymmetric hydrogenation require harsh conditions to convert them to amines. It has been stated that acetamides are 'worthless as protecting groups because the conditions required to remove them are harsh'.[6] From our own experience, we have seen removal of such acetates required prolonged exposure to 6 N HCl in refluxing MeOH. Consequently, we sought to develop a more practical enamide that could take advantage of the highly efficient asymmetric hydrogenation methods currently available. Aware of the clear advantages of trifluroacetate over acetate as a removable protecting group, we were hopeful that an extension of methodology could be made. A previous attempt to reduce an ene-trifluoroacetate with ruthenium catalysis was unsuccessful.[5] In that communication, the formyl group was employed to achieve milder deprotection. However, this protocol still required strongly basic conditions at elevated temperatures. Herein, we report our successful approach to developing a mild and practical route to enantioenriched amines via ene-trifluoroamides.

The benchmark synthesis of enamides reported by Burk utilized an iron mediated reduction of α-arylalkyl-oximes

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that are derived from the corresponding ketones.[7,8] This approach is an extension of Barton's earlier work.[9] To date, this reaction has only been applied to the synthesis of ene-acetamides.[4,10] Our modification to Burk's original enamide synthesis has led to a series of TFA-protected enamides in high overall yield. By simply substituting Ac_2O and HOAc with TFAA and TFA, ene-trifluoroacetamides **3** were generated in high overall yield (Table 1, entries a–f). Acetophenones bearing electron donating groups (entry g) were found to be problematic. Under the acidic reaction conditions, the oximes underwent a Beckmann rearrangement to form the corresponding amide.[11]

An alternative entry to ene-trifluoroacetamides is the Blaise reaction,[12] which occurs under non-acidic conditions, thereby providing a complimentary approach to the oxime approach.[13] Two examples, **5** and **3g**, have been generated from the corresponding nitrile via methyl addition and in situ trapping (Table 2). This protocol increased the overall yield of **3g** by twofold.

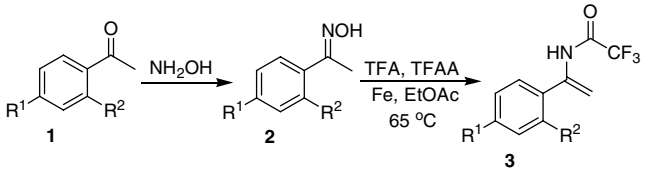
The literature is replete with examples of ene-acetamide asymmetric hydrogenations.[4] For most simple aromatic substrates, one can choose from a variety of chiral ligands to achieve the highest enantioselectivity for a given substitution pattern. Our objective was to determine and demonstrate that reductions of the ene-trifluroacetamides would provide comparable enantioselectivities with known performance ligands in this field.[14] Accordingly, we selected a well-established catalyst system for this purpose. Specifically, the MeBPE ligand originally described by Burk was employed in the demonstrations. Under standard reaction conditions, the hydrogenation of the ene-trifluroacetamides provided high yields and enantioselectivities in each case (Table 3). In comparison to the corresponding ene-acetamides cited in the literature,[7] the enantioselectivities derived from the reduction of the ene-trifluoroacetamides were within ±1.4% ee.

Recent findings in our laboratorys led us to evaluate a new application of the Josiphos ligands to the asymmetric hydrogenation of enamides.[15] The Josiphos derivatives **I** and **II** were found to reduce the ene-acetamide **5** to the acetamide **7** in 95.0% ee and 96.0% ee, respectively (Fig. 1).

To our knowledge, this is the first reported example of an asymmetric hydrogenation of an enamide using these ligands. A solvent screen with these ligands yielded the corresponding trifluoroacetamides with high enantioselectivity (Table 4). While ligand **I** was highly selective in both alcohol and the haloaromatic solvent 1,2-DCB, ligand **II** appeared to perform well only in 1,2-DCB. Additionally, only ligand **II** in 1,2-DCB reduced **3f** to the corresponding trifluoroamide with high enantioselectivity. Thus, subtle changes in ene-trifluoroamide structure can prompt changes in optimal ligand and solvent conditions

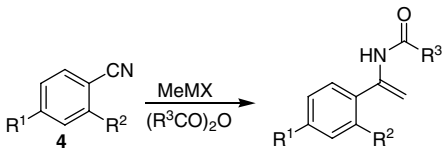
While pleased with the asymmetric hydrogenation results, we recognized that their utility could only be recognized and implemented for the synthesis of complex molecules if mild deprotection of the trifluoroacetamide was achieved as expected. To this end, the enantio-enriched trifluoroacetamides were treated with 2 equiv of K_2CO_3 in methanol at room temperature (Table 5). These deprotection conditions resulted in good to excellent yields of chiral amines.

Table 1. Synthesis of ene-trifluoroacetamides



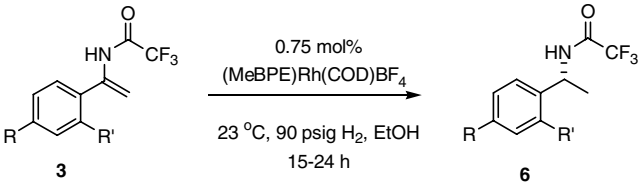
Entry	R^1	R^2	**2** (%)	**3** (%)
a	H	H	99	90
b	Br	H	100	93
c	CO_2Me	H	100	90
d	Ph	H	96	94
e	CF_3	H	100	96
f	Br	F	100	98
g	OMOM	H	95	26

Table 2. Enamide synthesis via Blaise reaction



R^1	R^2	R^3	MeMX	Yield	Product
Br	F	CH_3	MeMgBr	83	**5**
OMOM	H	CF_3	MeLi–LiBr	51	**3g**

Table 3. Asymmetric hydrogenation of ene-trifluoroacetamide with (MeBPE)Rh(COD)BF_4



Substrate	R^1	R^2	Conversion (yield)[a]	% ee of **6**	% ee of CH_3[b]
3a	H	H	>99 (80)[c]	96.5	95.2
3b	Br	H	>99 (91)	94.4	95.8
3c	CO_2Me[d]	H	>99 (95)	96.2	NDA[e]
3d	Ph	H	97 (94)	96.0	NDA[e]
3e	CF_3	H	>99 (98)	96.8	95.6
3f	Br	F	>99 (89)	98.3	NDA[e]
3g	OMOM	H	>99 (97)	97.6	NDA[e]

[a] Conversion is HPLC area percent conversion at 210 nm. Isolated yield in parentheses.
[b] Percent ee of the corresponding acetamide (with 0.2% catalyst) as reported in Ref. 4p.
[c] Assay yield = 95%.
[d] Reaction run in MeOH.
[e] NDA = no data available.