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# Synthesis of Enamides via Rh/C-Catalyzed Direct Hydroacylation of Ketoximes

**Zheng-Hui Guan,[‡] Kexuan Huang,[†] Shichao Yu,[†] and Xumu Zhang*[,†]**

*Department of Chemistry and Chemical Biology and Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854-8020, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

*xumu@rci.rutgers.edu*

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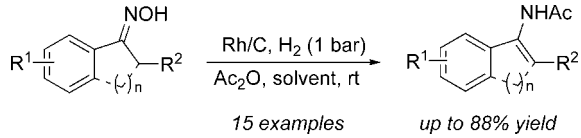
## ABSTRACT




**Enamides were efficiently prepared via a novel Rh/C-catalyzed direct hydroacylation of ketoximes. Up to 88% isolated yield of enamides were obtained with this method. Subsequent asymmetric hydrogenation of the enamides with Rh/DuanPhos complex gave the corresponding chiral amine in excellent enantioselectivities (up to 99.7% ee).**

Enamides and their derivatives are versatile synthetic intermediates in synthetic organic chemistry for the preparation of chiral amines, amino acids, and various heterocyclic compounds.[1] Furthermore, the enamide moiety is also a key substructure in various classes of natural products and pharmaceutical drug lead compounds.[2] In the past decade, we have been interested in the development of asymmetric hydrogenation for the synthesis of enantiomerically pure amines from enamides.[3] However, the synthesis of the required highly substituted enamide precursors in an efficient manner is still a challenge.

Conventionally, protocols for the preparation of enamides mainly consist of (1) direct condensation of amides with ketones,[4] (2) transition-metal-catalyzed coupling of vinyl derivatives with amide,[5] and (3) reaction of N−H imines derived from ketones or nitriles with appropriate electrophiles.[6] Although successful in a limited number of cases, direct condensation of a ketone with an amide to provide an enamide is not a general transformation. The transition-metal-catalyzed coupling reactions require additional steps to form the necessary vinyl substrates or access to the properly functionalized coupling

[†] Rutgers University.
[‡] Lanzhou University.

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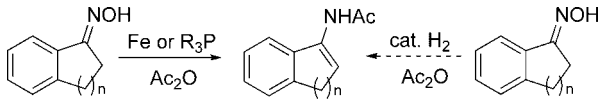
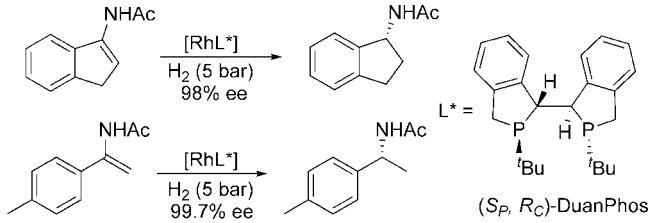
partners, although they appear to be a reliable approach to the stereoselective preparation of enamides. The addition of an organometallic to a nitrile is a direct approach, but this method is usually not preferred because of complex reaction mixtures and low yields. Burk et al. and our group reported the reductive acylation of ketoximes with iron in the presence of $Ac_2O$ to prepare enamides.[7] This approach was often the method of choice at smaller scale. An alternative approach recently reported by Singh and co-workers involves a phosphine-mediated reductive acylation of ketoximes,[8] but an atom-economical and environmentally benign approach to construct enamides would be the direct hydroacylation of ketoximes (outlined in Scheme 1).

**Scheme 1**



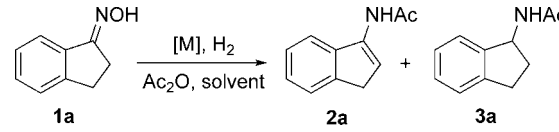

There is only limited precedent for the hydroacylation of ketoximes to date.[9] The most general procedure was recently published by Burgos et al. for the reductive acylation of ketoximes using Ir/C and Rh/C as catalysts.[9a] However, the reaction generally needs high temperature to proceed and gives low yields of electron-rich indanone oximes. In this communication, we have improved the synthetic method and developed an efficient catalytic process for the Rh/C-catalyzed hydroacylation of ketoximes. This process proceeds at room temperature and gives the corresponding enamides in high yields.

**Scheme 2.** Asymmetric Hydrogenation of Enamides




Our experiment was initially conducted by treating indanone oxime **1a** with $Ac_2O$ in toluene. A variety of transition metal catalysts were screened in the presence of $H_2$ (1 bar) (Table 1). To our delight, Rh/C shows particularly

**Table 1.** Optimization of Hydrogenation Acylation of Ketoxime[a]




| entry | catalyst | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | Pd/C | toluene | tr (90) |
| 2 | Rh/C | toluene | 83 (0) |
| 3 | $Rh/Al_2O_3$ | toluene | 78 (0) |
| 4 | Ru/C | toluene | 10 (0) |
| 5 | $PtO_2$ | toluene | tr (95) |
| 6 | $Pd/BaSO_4$ | toluene | tr (0) |
| 7 | $Pd/CaCO_3$ | toluene | tr (0) |
| 8 | Raney Ni | toluene | tr (0) |
| 9 | Rh/C | EtOH | 88 (0) |
| 10 | Rh/C | $CH_2Cl_2$ | 85 (0) |
| 11 | Rh/C | THF | 72 (0) |
| 12 | Rh/C | EtOAc | 56 (0) |
| 13 | Rh/C | $Ac_2O$ | 63 (0) |

[a] Reaction conditions: **1a** (0.2 mmol), $Ac_2O$ (3 equiv), catalyst (0.5 mol %), $H_2$ (1 bar), in solvent (2 mL) at rt for 10 h. [b] Isolated yield; tr = trace. [c] The numbers in parentheses are the isolated yields of **3a**.

remarkable reactivity, and 83% yield of the desired enamide **2a** was obtained in this transformation (Table 1, entry 2). $Rh/Al_2O_3$ was also effective (Table 1, entry 3), but very low conversion was observed when Ru/C, $Pd/BaSO_4$, $Pd/CaCO_3$, or Raney Ni was employed as the catalyst (Table 1, entries 4, 6−8). Furthermore, when Pd/C or $PtO_2$ was used as catalyst, the major product was the amide **3a** (Table 1, entries 1, 5). Optimization of the solvent revealed that EtOH, toluene, and $CH_2Cl_2$ were superior to THF and EtOAc (Table 1, entries 2, 9−12). $Ac_2O$ could also be directly used as solvent, but the desired enamide **2a** was only obtained in moderate yield (Table 1, entry 13). In addition, the pressure of hydrogen did not have a significant effect on the yield of the transformation.

Having gained an understanding of the factors that influence the hydroacylation of the ketoxime process, we explored the scope of this method (Table 2). The ketoximes were in all cases prepared from the corresponding ketones on the basis of literature precedence[8,10] and used in the reaction without further purification.

Various indanone-derived ketoximes gave good yields of enamide. Electron-rich indanone ketoximes show good reactivity and gave high yields of the corresponding enamides **2b,c** (Table 2, entries 2 and 3), and a tetrasubstituted cyclic enamide **2d** can also be obtained in a high yield (Table 2, entry 4). An extensive investigation of the reaction shows that α-tetralones-derived ketoximes **1e**−**i** also worked well when toluene/$Ac_2O$ was employed as the solvent, and high yields of the desired

(6) (a) Savarin, C. G.; Boice, G. N.; Murry, J. A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* **2006**, *8*, 3903, and references therein. (b) Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003. (c) Burk, M. J.; Lee, J. R.; Wang, Y. M. *J. Am. Chem. Soc.* **1996**, *118*, 5142. (d) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron* **1995**, *6*, 349.

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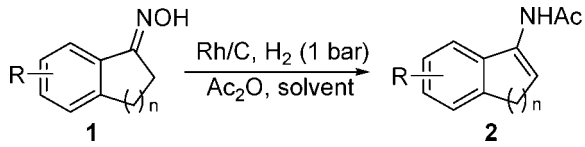
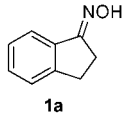
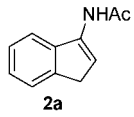
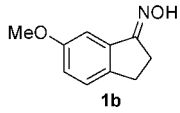
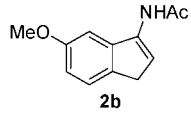
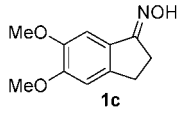
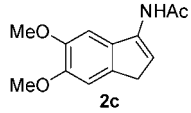
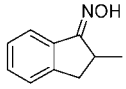
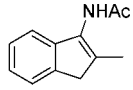
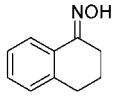
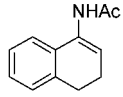
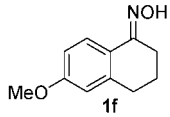
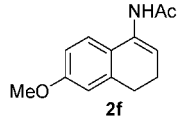
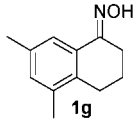
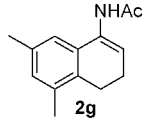
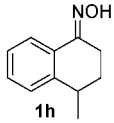
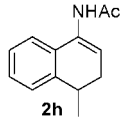
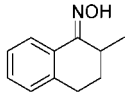
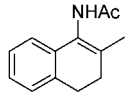
(10) For standard protocol see: Bousquet, E. W.; Carothers, W. H.; McEwen, W. L. *Organic Synthesis*; Wiley: New York, 1943; *Collect. Vol. II*, pp 313−315. For a specific procedure, see: Homes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

**Table 2.** Rh/C-Catalyzed Hydrogenation Acylation of Cyclic Ketoximes[a]




1 2

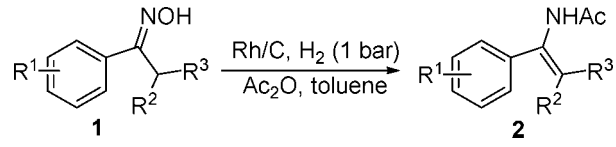
| entry | ketoxime **1** | enamide **2** | yield (%)[b] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 88 |
| 2 |  **1b** |  **2b** | 82 |
| 3 |  **1c** |  **2c** | 81 |
| 4 |  **1d** |  **2d** | 82 |
| 5 |  **1e** |  **2e** | 85[c] |
| 6 |  **1f** |  **2f** | 81[c] |
| 7 |  **1g** |  **2g** | 78[c] |
| 8 |  **1h** |  **2h** | 82[c] |
| 9 |  **1i** |  **2i** | 83[c] |

[a] Reaction conditions: **1** (0.2 mmol), $Ac_2O$ (3 equiv), Rh/C (0.5 mol %), $H_2$ (1 bar), in EtOH (2 mL) at rt for 10 h. [b] Isolated yield. [c] Rh/C (1 mol %), toluene/$Ac_2O$ (v/v = 4/1) (2 mL) was used as solvent.

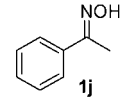
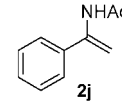
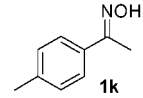
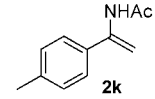
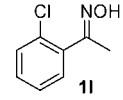
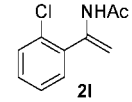
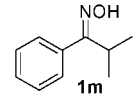
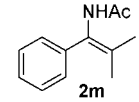
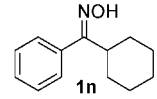
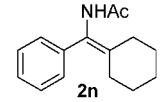
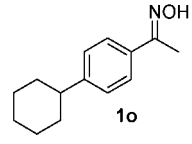
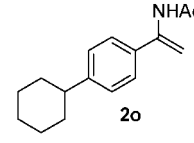
enamides were obtained in these transformations. These results were also superior to those obtained by using iron powder or triethylphosphine as the reductant.[7,8]

For extending the substrate scope, we have investigated the reactions of acyclic ketoximes as well (Table 3). Satisfactorily, the hydroacylation proceeded smoothly. A variety of arene substituents, including Me and sensitive Cl functionality, were well tolerated in these transformations (Table 3, entries 2 and 3). The desired enamides, even the tetrasubstituted enamides **2m,n**, were achieved in good yields.

**Table 3.** Rh/C-Catalyzed Hydrogenation Acylation of Acyclic Ketoximes[a]




1 2

| entry | ketoxime **1** | enamide **2** | yield (%)[c] |
|---|---|---|---|
| 1 |  **1j** |  **2j** | 65 |
| 2 |  **1k** |  **2k** | 62 |
| 3 |  **1l** |  **2l** | 57 |
| 4 |  **1m** |  **2m** | 68 |
| 5 |  **1n** |  **2n** | 70 |
| 6 |  **1o** |  **2o** | 66 |

[a] Reaction conditions: **1** (0.2 mmol), Rh/C (1 mol %), $H_2$ (1 bar), in toluene/$Ac_2O$ (v/v = 4/1) (2 mL) at rt for 10 h. [b] Isolated yield.

In a related manner, these enamides can be easily transformed via an asymmetric hydrogenation step with Rh-DuanPhos complex to afford the corresponding chiral amines (with 100% conversion and up to 99.7% ee), the key intermediates for drugs (Scheme 2).

In summary, we have developed a mild and general procedure for the Rh/C-catalyzed direct hydroacylation of ketoximes for preparation of enamides. This method combined with the related asymmetric hydrogenation provides a practical protocol for the synthesis of chiral amines. Current research is focused on extending the scope and the asymmetric hydrogenation of more challenging tetrasubstituted enamides. This progress will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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