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# Rapid Construction of (-)-Paroxetine and (-)-Femoxetine via *N*-Heterocyclic Carbene Catalyzed Homoenolate Addition to Nitroalkenes

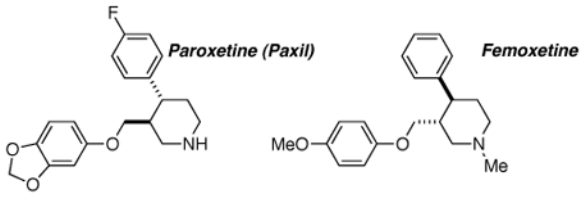
**Nicholas A. White**, **Kerem E. Ozboya**, **Darrin M. Flanigan**, and **Tomislav Rovis**
Department of Chemistry, Colorado State University, Fort Collins, CO 80523 (USA), Fax: (+)

Tomislav Rovis: rovis@lamar.colostate.edu

## Abstract

A concise enantioselective synthesis of (-)-paroxetine (*Paxil*) and (-)-femoxetine has been achieved. Key to these syntheses is a *N*-heterocyclic carbene catalyzed homoenolate addition to a nitroalkene followed by in situ reduction of the nitro-group to rapidly access δ-lactams.

Due to their abundance in natural products and medicinal agents, the rapid, stereodefined construction of piperidines has received considerable attention from the synthetic community. [1, 2] Specifically, the pursuit of methodologies to furnish 3- and 4- substituted piperidine rings has been the subject of particularly intense focus due to its application in the synthesis of paroxetine. Paroxetine (Paxil) is a selective serotonin reuptake inhibitor (SSRI) that was discovered in 1970 and introduced to market in 1992 as a treatment for depression, anxiety, and panic disorder. [3] A related SSRI, femoxetine, was discovered concurrently with paroxetine, but was not pursued.[3]




Since the initial report, many syntheses of paroxetine have appeared relying upon the establishment of a single enantiomer of *N*-protected *trans*-4-(4-fluorophenyl)-3-piperidinemethanol **II**, followed by coupling with sesamol and deprotection. Approaches to set the stereochemistry often depend on the chiral pool, [4] resolution, [5] chiral auxiliaries, [6] chiral base, [7] and asymmetric catalysis. [8] These methods have proven effective and are represented in the literature accordingly. However, a highly convergent synthesis in which all the carbons of paroxetine are introduced in a single stereocontrolled step is lacking.

Recently, we reported a *N*-heterocyclic carbene (NHC) catalyzed homoenolate addition of enals to nitroalkenes allowing access to syn δ-nitroesters in good yield, excellent dr, and

Correspondence to: Tomislav Rovis, rovis@lamar.colostate.edu.
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excellent ee.[9,10] Furthermore, we developed a protocol for the in situ reduction of the *syn* δ-nitroesters to the corresponding *trans* δ-lactam. This method provides rapid access to *trans* 3,4-disubstituted piperidones. We envisioned that utilization of this method would allow for exceptional levels of efficiency in the syntheses of paroxetine and femoxetine. Our method is notable, as it allows for the concomitant formation of the piperidine ring and establishment of the contiguous stereocenters in a single reaction (Scheme 1).

We began our synthesis of paroxetine by forming requisite nitro alkene **3** (Scheme 2). From commercially available aldehyde **2** we performed a Henry reaction with nitromethane followed by elimination with trifluoroacetic anhydride to furnish nitroalkene **3** in 68 % yield over two steps. With this nitroalkene in hand we were ready to attempt the key NHC-catalyzed step. Using conditions we optimized and reported in our previous publication using catalyst **1a** we observed no desired lactam product **5**. We hypothesized that the bulky bis-butyl/OTMS moiety of the catalyst may be too large to facilitate the reaction and explored other catalyst scaffolds (Table 1). We found that fluorinated catalyst **1b**[11] provides the desired lactam **5** in 82 % ee, 10:1 dr, and 58 % yield. Satisfied with these results we scaled the reaction to 9 mmol and were pleased to find the reaction proceeds smoothly, delivering 1.8 grams of product in predictable yield and selectivities. We then subjected 1.2 grams (3.55 mmol) of the lactam precursor **5** to a LAH reduction, which delivered paroxetine (*Paxil*) **6** in 88 % yield (1.0 grams, 3.13 mmol), for an overall yield of 35 % over 4 steps in 82 % ee.

Due to its structural similarity with paroxetine, we also explored a short synthesis of femoxetine. We first synthesized nitroalkene **8** from a two-step Henry/elimination sequence to furnish nitroalkene **8** in 20 % yield over two steps (Scheme 3). We then subjected nitroalkene **8** and cinnamaldehyde to the key NHC-catalyzed step followed by in situ reduction and were pleased to observe lactam **10** in 53 % yield, 7:1 dr, and 82 % ee. Methylation of the lactam with methyl iodide followed by LAH reduction completes our synthesis of femoxetine **11** in 5 steps and 82 % ee.

In conclusion, we have developed rapid syntheses of (-)-paroxetine and (-)-femoxetine by employing a NHC catalyzed coupling of enals and nitroalkenes. The use of fluorinated NHC catalyst **1b** in a one-pot sequence provides access to lactam products in moderate yield and good stereoselectivities, which were quickly elaborated to both paroxetine and femoxetine. Further, we have demonstrated that this approach is amenable to gram scale. To the best of our knowledge, this work represents the shortest synthesis of paroxetine to date.

## Experimental Section

Preparation of Lactam **5**: To a 100 mL flame dried round bottom flask containing a magnetic stirbar was added nitroalkene **3** (2.01 g, 9 mmol, 1.0 equiv), NHC **1b** (377 mg, 0.9 mmol, 10 mol%), sodium acetate (370 mg, 4.5 mmol, 0.5 equiv), 4-fluorocinnamaldehyde (2.03 g, 13.5 mmol, 1.5 equiv), followed by 30 mL ethanol. The flask was then fitted with a rubber septum and stirred under an atmosphere of argon for 12 hours at 23 °C. After 12 hours, the septum was removed and zinc dust (5.85 g, 90 mmol, 10 equiv) was added followed by 30 ml of acetic acid. The flask was then heated under reflux with a reflux condenser and

heating mantle. After four hours, the heat source was removed and the reaction was allowed to cool. Upon cooling, the reaction was filtered through celite and rinsed with 30 mL EtOAc. The filtrate was then diluted with an additional 20 mL EtOAc and quenched with 60 mL saturated $NaHCO_3$. The organic layer was then separated, washed with brine (1 × 60 mL), dried ($Na_2SO_4$), and concentrated *in vacuo*. The crude residue was then purified by column chromatography (5 % MeOH in $CH_2Cl_2$) to yield 58 % (4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-2-one as an off-white solid (82% ee, 10:1 dr).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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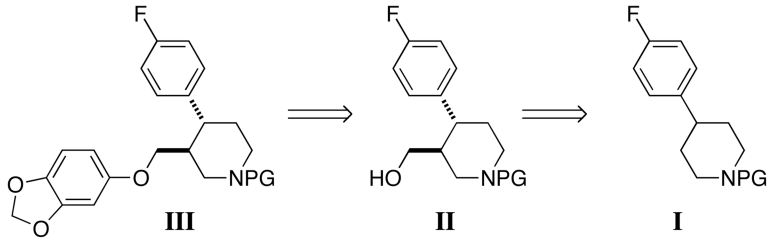
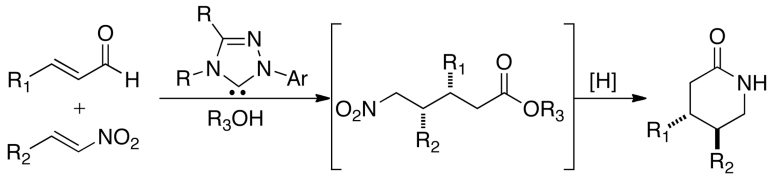
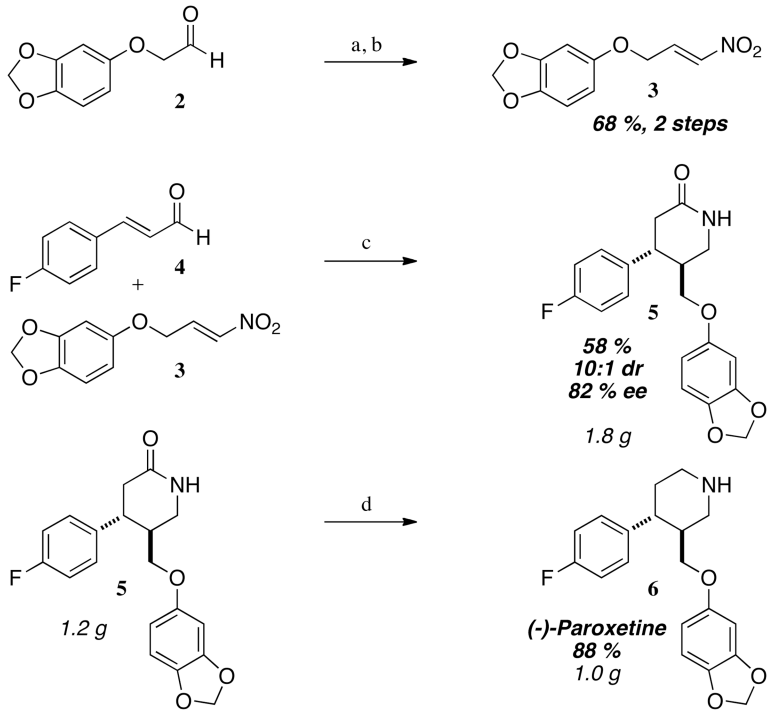



**Figure 1. Typical Synthetic Approach Towards Paroxetine**

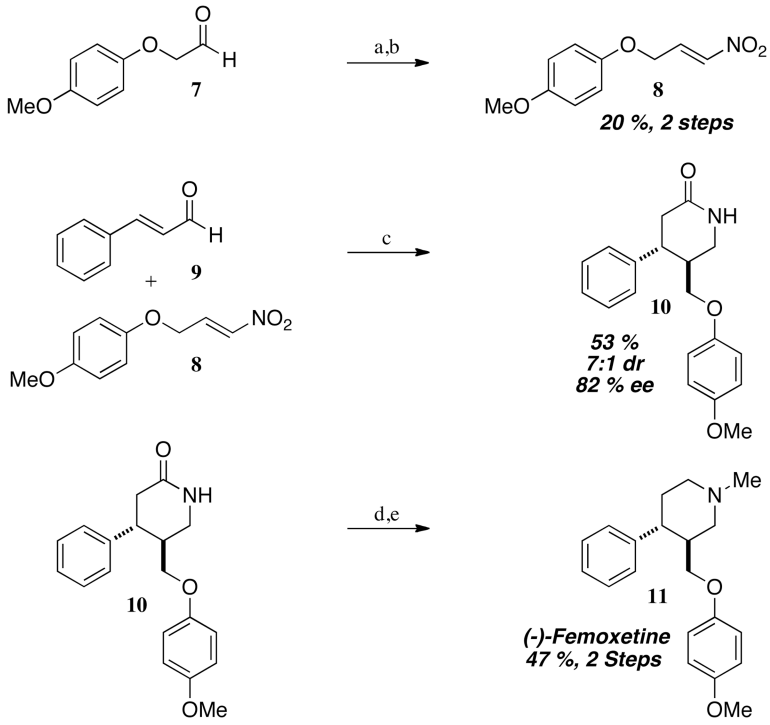



**Scheme 1. NHC-Catalyzed Nitroester/Lactam Formation**




**Scheme 2.**

Preparation of paroxetine. Reagents and conditions: a) $CH_3NO_2$, KO*t*Bu (20 mol%), *t*BuOH/THF, 0 to 23 °C, quantitative; b) trifluoroacetic anhydride, $Et_3N$, $CH_2Cl_2$, 0 °C, 68 %; c) NHC **1b**, NaOAc (50 mol%), EtOH, 23 °C, 12 h, then Zn (dust), EtOH/AcOH, reflux, 58 %, 10:1 dr, 82 % ee; d) $LiAlH_4$, THF, 0 to 66 °C, 88 %.

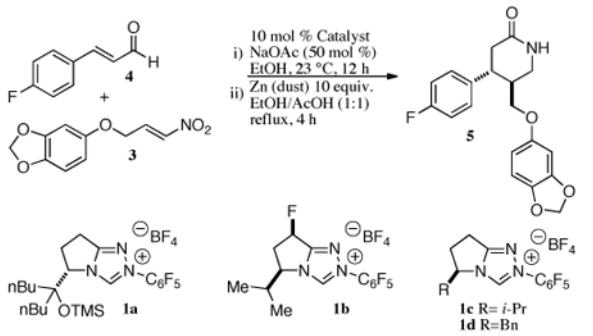



**Scheme 3.**

Preparation of femoxetine. Reagents and conditions: a) $CH_3NO_2$, KO*t*Bu (20 mol%), *t*BuOH/THF, 0 to 23 °C, quantitative; b) trifluoroacetic anhydride, $Et_3N$, $CH_2Cl_2$, 0 °C, 20 %; c) NHC **1b**, NaOAc (50 mol%), EtOH, 23 °C, 12 h, then Zn (dust), EtOH/AcOH, reflux, 53 %, 7:1 dr, 82 % ee; d) NaH, $CH_3I$, THF, 23 °C, 55 %; e) $LiAlH_4$, THF, 0 to 66 °C, 87 %.

## Table 1

Chiral Catalyst Screen.




| Entry | Catalyst | yield[a] | dr (*trans/cis*)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **1a** | - | N/A | N/A |
| 2 | **lb** | 58 | 10:1 | 82 |
| 3 | **1c** | 48 | 8:1 | 71 |
| 4 | **1d** | 51 | 7:1 | 69 |

[a] Yields are isolated yields after chromatography.

[b] Diastereoselectivity determined by $^1$H NMR of the unpurified reaction mixture.

[c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.