

Enantioselective Organocatalytic Michael Additions of Aldehydes to Enones with Imidazolidinones: Co-Catalyst Effects and Evidence for an Enamine Intermediate

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Supporting Information

General Procedures. Analytical thin-layer chromatography was carried out on Whatman TLC plates precoated with silica gel 60 (250 μm thickness). Visualization was performed using a UV lamp or potassium permanganate stain. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh).

Materials. Commercial reagents were purchased from Sigma Aldrich, and used as received with the following exception: hydrocinnamaldehyde and octyl aldehyde were distilled prior to use.

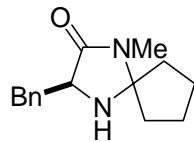
Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AC-300 (300 MHz) or Varian Inova-500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer. Mass spectra (MS) were obtained using an electrospray ionization (ESI) mass spectrometer or an electron impact (EI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 241 digital polarimeter and are reported as follows: $[\alpha]_{\text{D}}^{\text{rt}}$ (c in g per 100 mL, solvent). The enantiomeric excess (ee) of the products was determined by chiral GC or HPLC analysis of either the corresponding 5-keto carboxylic acids (obtained after Jones oxidation) or the corresponding 5-keto cyclic acetals (obtained after the selective protection of aldehyde) (see below for the general procedures). Chiral GC analysis was performed on a Shimadzu GC-17A gas chromatograph. Chiral HPLC analysis was performed on a Shimadzu 10A instrument.

The MacMillan imidazolidinone, (5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride (**1a-HCl**), was prepared using the literature method.¹ The free base could be isolated by dissolving the salt in sat. NaHCO_3 , extracting into CH_2Cl_2 (3x), drying over Na_2SO_4 , and concentrating *in vacuo*. Imidazolidinones **1b-d** were prepared using the analogous procedure using the appropriate ketone and purified as described below:

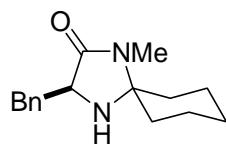
(S)-5-Benzyl-2,2-dibutyl-3-methyl-imidazolidin-4-one (1b) was purified by Kugelrohr distillation of the excess 5-nonenone to yield 1b as a colorless oil. The HCl salt of this imidazolidinone was not crystalline and thus could not be recrystallized: $[\alpha]_{\text{D}}^{\text{rt}} = -58.3^\circ$ ($c = 1.4$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ

¹ Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *120*, 4243.

7.20-7.33 (m, 5H), 3.82 (t, $J = 5.5$ Hz, 1H), 3.02-3.15 (m, 2H), 2.67 (s, 3H), 1.08-1.70 (m, 11H), 0.87 (t, $J = 7.2$ Hz, 3H), 0.78 (t, $J = 7.2$ Hz, 3H), 0.55-0.73 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): 174.0, 137.5, 130.0, 128.8, 127.0, 80.2, 60.2, 39.1, 37.8, 37.5, 25.5, 25.5, 24.2, 23.0, 22.8, 14.2, 14.1; TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 303.2, found 303.3.



(S)-3-Benzyl-1-methyl-1,4-diaza-spiro[4.4]nonan-2-one (1c) was isolated by precipitation of the HCl salt from isopropanol upon addition of hexanes. The crude product could be recrystallized by dissolving it in a minimum volume of hot isopropanol, adding hexanes slowly with heating until cloudiness persists, and then adding a minimum volume of isopropanol until the solution becomes homogeneous again: $[\alpha]_{\text{D}}^{\text{rt}} = -78.4^\circ$ ($c = 1.2$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.20-7.34 (m, 5H), 3.73 (t, $J = 5.5$ Hz, 1H), 3.13 (dd, $J = 14.1, 4.5$ Hz, 1H), 3.04 (dd, $J = 14.4, 6.6$ Hz, 1H), 2.76 (s, 3H), 1.83-1.94 (m, 1H), 1.60-1.80 (m, 7H), 1.16-1.23 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): 174.1, 137.4, 129.7, 128.6, 126.8, 85.9, 59.6, 37.0, 36.9, 34.8, 25.5, 24.0, 23.9; TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 245.2, found 245.3.



(S)-3-Benzyl-1-methyl-1,4-diaza-spiro[4.5]decan-2-one (1d) was purified by recrystallization of the HCl salt using an isopropanol/hexanes mixed solvent system: $[\alpha]_{\text{D}}^{\text{rt}} = -76.5^\circ$ ($c = 1.0$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.19-7.34 (m, 5H), 3.76 (dd, $J = 6.3, 4.2$ Hz, 1H), 3.12 (dd, $J = 13.8, 4.5$ Hz, 1H), 2.99 (dd, $J = 13.8, 6.6$ Hz, 1H), 2.75 (s, 3H), 1.40-1.70 (m, 9H), 0.89-1.23 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): 173.7, 137.7, 129.8, 128.6, 126.8, 77.5, 59.3, 38.1, 36.5, 33.8, 25.4, 25.0, 22.7, 22.2; TOF-MS-ESI: $[\text{M}+\text{H}]^+$ calculated 259.2, found 259.3.

General Procedure 1: Catalytic asymmetric Michael addition to vinyl ketones. To a 1 dram vial equipped with a magnetic stirring bar was add the catalyst (0.2 equiv) and ethyl 3,4-dihydroxybenzoate (0.2 equiv.). The vinyl ketone (3.0 equiv.) and aldehyde (1.0 equiv.) were added via syringe and the reactions were stirred at room temperature for 20 h. The crude reaction mixture was directly purified by flash column chromatography on silica gel using either hexane/ethyl acetate or pentane/ether mixtures.

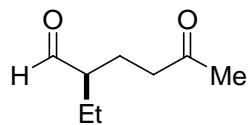
General Procedure 2: Preparation of carboxylic acids by Jones oxidation.² To pure keto aldehyde in ether cooled in a bath of cold water was added an aqueous solution of Jones reagent. The cold water bath was removed and the reaction was stirred for 2-18h. The ether layer was separated and the aqueous layer was extracted with ether (3x). The combined ether layers were extracted with 3M NaOH (3x). The base extracts were acidified with 3M HCl until pH 2. The product was extracted into ether, dried over MgSO_4 , and concentrated *in vacuo*. ^1H NMR confirmed that complete oxidation to the carboxylic acid had occurred.

General Procedure 3: Preparation of cyclic acetals by selective acetalization of the aldehyde.³ Pure keto aldehydes were dissolved in CH_2Cl_2 followed by the addition of 1.1 equiv of propane-1,3-diol and a catalytic amount of *p*-toluensulfonic acid (0.1 equiv). After being stirred for 16 h, the reaction mixture was quenched with NaHCO_3 . The layers were separated and

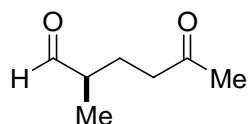
² Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, 56, 3286.

³ Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, 68, 4151.

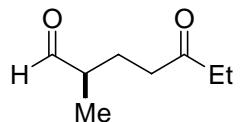
the aqueous layer was extracted with CH_2Cl_2 (2x), and dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. ^1H NMR showed that selective protection of the aldehyde functionality occurred with high chemoselectivity.



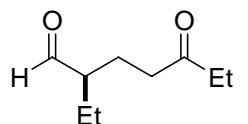
(R)-2-Ethyl-5-oxo-hexanal (4)⁴ was prepared by the General Procedure 1 using 50.5 mg of **1c** (0.207 mmol), 37.7 mg of ethyl 3,4-dihydroxybenzoate (0.207 mmol), 254 μL of methyl vinyl ketone (3.10 mmol), and 93 μL of butyraldehyde (1.04 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.27$, 7:3 hexanes:EtOAc) to afford 117 mg of the desired product as a colorless oil (0.825 mmol, 79%). $[\alpha]^{rt}_D = -3.2^\circ$ ($c = 1.4$, CHCl_3 , 89% ee). The product was converted to the corresponding carboxylic acid using General Procedure 2 and the enantiomers were separated by chiral GC with use of a Supelco β -Dex 120 column: T1) 90 °C, 10 min; T2) 130 °C, 2 °C/min; T3) 160 °C, 1 °C/min; T_{R1} : 55.1 min (minor), T_{R2} : 55.5 min (major).



(R)-2-Methyl-5-oxo-hexanal (Table 3, entry 1)⁵ was prepared by the General Procedure 1 using 50.5 mg of **1c** (0.207 mmol), 37.7 mg of ethyl 3,4-dihydroxybenzoate (0.207 mmol), 254 μL of methyl vinyl ketone (3.10 mmol), and 75 μL of propionaldehyde (1.03 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.19$, 7:3 hexanes:EtOAc) to afford 111 mg of the desired product as a colorless oil (0.862 mmol, 84%). $[\alpha]^{rt}_D = +0.7^\circ$ ($c = 1.3$, CHCl_3 , 90% ee). The product was converted to the corresponding carboxylic acid using General Procedure 2 and the enantiomers were separated by chiral GC with use of a Supelco β -Dex 120 column: T1) 90 °C, 10 min; T2) 130 °C, 2 °C/min; T3) 160 °C, 1 °C/min; T_{R1} : 49.0 min (minor), T_{R2} : 49.7 min (major).



(R)-2-Methyl-5-oxo-heptanal (Table 3, entry 2)³ was prepared by the General Procedure 1 using 54.4 mg of **1c** (0.223 mmol), 40.6 mg of ethyl 3,4-dihydroxybenzoate (0.223 mmol), 331 μL of ethyl vinyl ketone (3.34 mmol), and 81 μL of propionaldehyde (1.11 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.29$, 7:3 hexanes:EtOAc) to afford 112 mg of the desired product as a colorless oil (0.788 mmol, 71%). $[\alpha]^{rt}_D = -2.2^\circ$ ($c = 0.93$, CHCl_3 , 92% ee). The product was converted to the corresponding carboxylic acid using General Procedure 2 and the enantiomers were separated by chiral GC with use of a Supelco β -Dex 120 column T1) 90 °C, 10 min; T2) 130 °C, 2 °C/min; T3) 160 °C, 1 °C/min; T_{R1} : 55.1 min (minor), T_{R2} : 55.9 min (major).

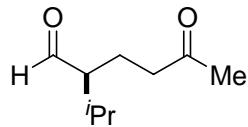


(R)-2-Ethyl-5-oxo-heptanal (Table 3, entry 3)³ was prepared by the General Procedure 1 using 52.8 mg of **1c** (0.216 mmol), 39.0 mg of ethyl 3,4-dihydroxybenzoate (0.216 mmol), 321 μL of ethyl vinyl ketone (3.24 mmol), and 97 μL of butyraldehyde (1.08 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.40$, 8:2 hexanes:EtOAc) to afford 114 mg of the desired product as a colorless oil (0.734 mmol, 68%).

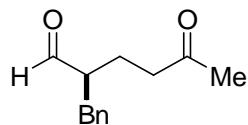
⁴ Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777.

⁵ Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.

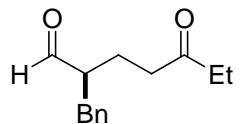
$[\alpha]^{rt}_D = +8.2^\circ$ ($c = 1.2$, CHCl_3 , 92% ee). The product was converted to the corresponding carboxylic acid using General Procedure 2 and the enantiomers were separated by chiral GC with use of a Supelco β -Dex 120 column: T1) 100°C , 0 min; T2) 140°C , $1^\circ\text{C}/\text{min}$; T3) 200°C , $2^\circ\text{C}/\text{min}$; T_R1 : 55.2 min (minor), T_R2 : 55.6 min (major).



(S)-2-Isopropyl-5-oxo-hexanal (Table 3, entry 4)^{6,7} was prepared by the General Procedure 1 using 45.7 mg of **1c** (0.187 mmol), 34.1 mg of ethyl 3,4-dihydroxybenzoate (0.187 mmol), 230 μL of methyl vinyl ketone (2.81 mmol), and 100 μL of isovaleraldehyde (0.936 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.34$, 7:3 hexanes:EtOAc) to afford 80 mg of the desired product as a colorless oil (0.51 mmol, 55%). $[\alpha]^{rt}_D = +24^\circ$ ($c = 1.8$, CHCl_3 , 82% ee). The product was converted to the corresponding carboxylic acid using General Procedure 2 and the enantiomers were separated by chiral GC with use of a Supelco β -Dex 120 column: T1) 100°C , 0 min; T2) 140°C , $1^\circ\text{C}/\text{min}$; T3) 200°C , $2^\circ\text{C}/\text{min}$; T_R1 : 53.6 min (minor), T_R2 : 53.9 min (major).



(S)-2-Benzyl-5-oxo-hexanal (Table 3, entry 6)⁶ was prepared by the General Procedure 1 using 58.1 mg of **1c** (0.238 mmol), 43.4 mg of ethyl 3,4-dihydroxybenzoate (0.238 mmol), 293 μL of methyl vinyl ketone (3.57 mmol), and 157 μL of butyraldehyde (1.19 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.21$, 8:2 hexanes:EtOAc) to afford 151 mg of the desired product as a colorless oil (0.737 mmol, 62%). $[\alpha]^{rt}_D = -0.37^\circ$ ($c = 1.6$, CHCl_3 , 89% ee). The product was converted to the corresponding propanediol monoacetal using General Procedure 3 and the enantiomers were separated by HPLC using a Chiracel OD column (85/15 hexane/*i*-PrOH; flow rate 0.5 mL/min; T_R1 : 30.2 min (major), T_R2 : 36.7 min (minor).



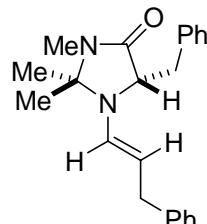
(S)-2-Benzyl-5-oxo-heptanal (Table 3, entry 7)⁶ was prepared by the General Procedure 1 using 49.1 mg of **1c** (0.201 mmol), 36.6 mg of ethyl 3,4-dihydroxybenzoate (0.201 mmol), 299 μL of ethyl vinyl ketone (3.02 mmol), and 133 μL of hydrocinnamaldehyde (1.01 mmol). The crude product was purified by flash chromatography with pentane/Et₂O (80:20 followed by 70:30, $R_f = 0.33$, 8:2 hexanes:EtOAc) to afford 120 mg of the desired product as a colorless oil (0.550 mmol, 54%). $[\alpha]^{rt}_D = -1.7^\circ$ ($c = 1.9$, CHCl_3 , 92% ee). The product was converted to the corresponding propanediol monoacetal using General Procedure 3 and the enantiomers were separated by HPLC using a Chiracel OD column (92/8 hexane/*i*-PrOH; flow rate 1.0 mL/min; T_R1 : 19.0 min (major); T_R2 : 23.7 min (minor).

Assignment of keto aldehyde stereochemistry: The absolute stereochemistry was assigned for (S)-2-isopropyl-5-oxo-hexanal by comparing the sign of the optical rotation to the same compound reported in the literature, which had been synthesized from limonene.⁷ All other compounds were assigned by analogy to this compound. The GC profile of the carboxylic acids

⁶ Hagiwara, H.; Komatsubara, N.; Ono, H.; Okabe, T.; Hoshi, T.; Suzuki, T.; Ando, M.; Kato, M. *J. Chem. Soc. Perkin Trans. 1* **2001**, 316.

⁷ Hudlicky, T.; Fleming, A.; Radescu, L. *J. Am. Chem. Soc.* **1989**, 111, 6691.

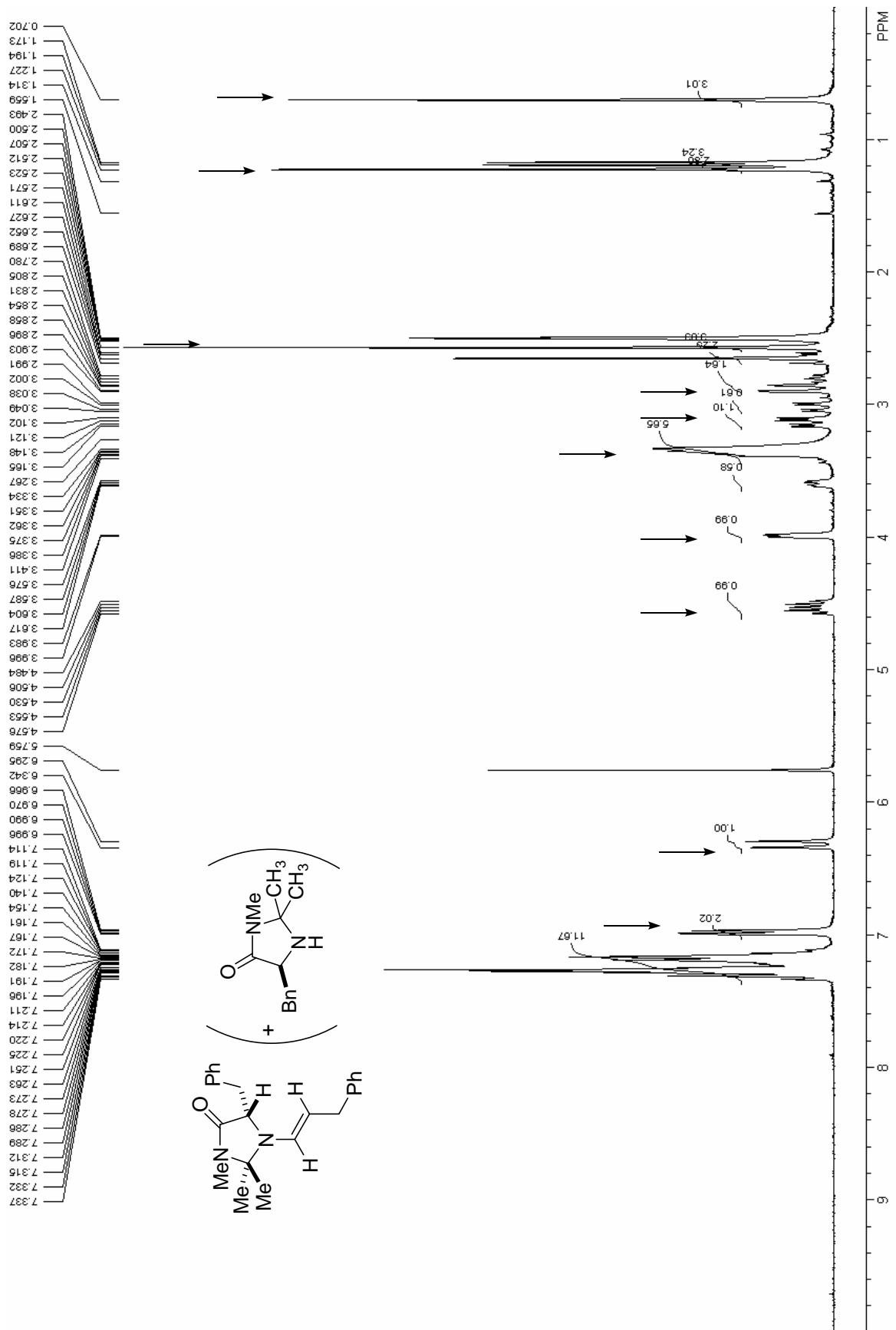
derived from related keto aldehydes matched that observed for the carboxylic acid derived from (*S*)-2-isopropyl-5-oxo-hexanal (minor enantiomer eluting first). It should be noted that in two cases (**4** and (*R*)-2-methyl-5-oxo-heptanal) the optical rotations we measured were of the opposite sign relative to those reported for the same enantiomer by Jørgensen.³ However, in these cases the magnitudes of the rotations were very small, and the differences may be within experimental error.

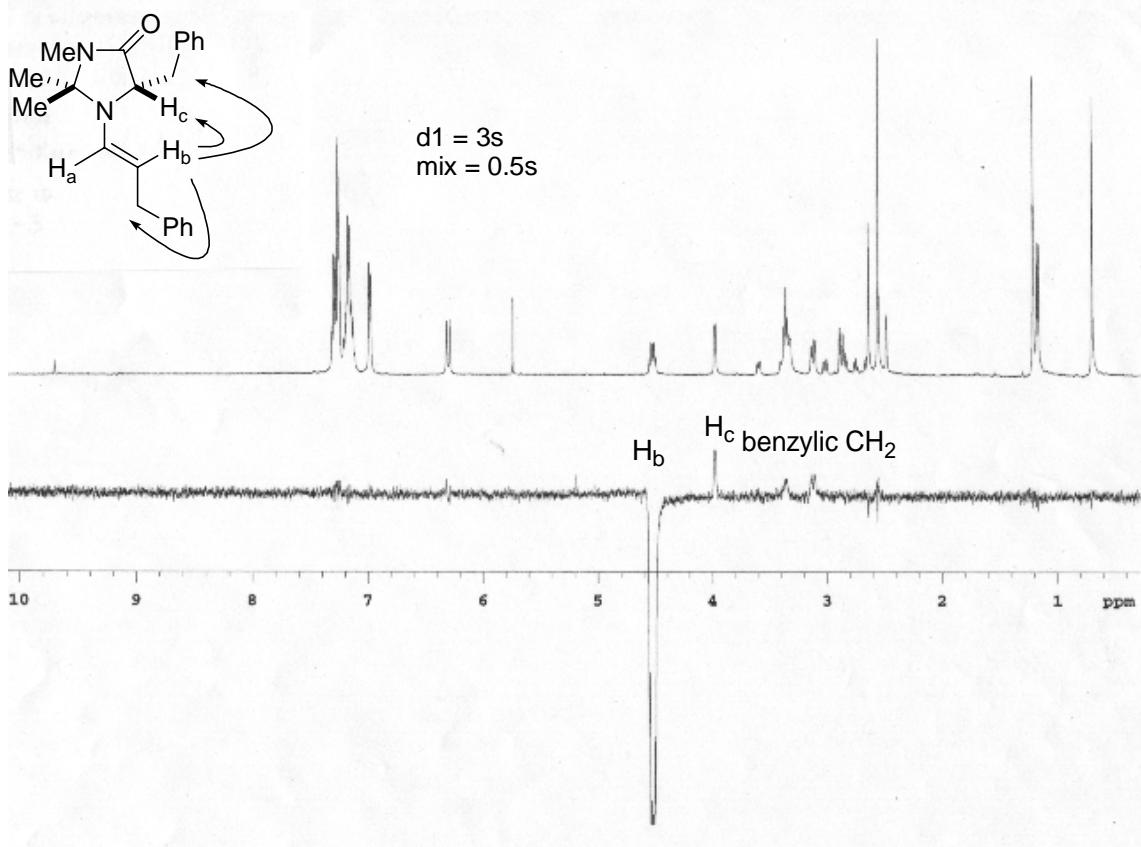
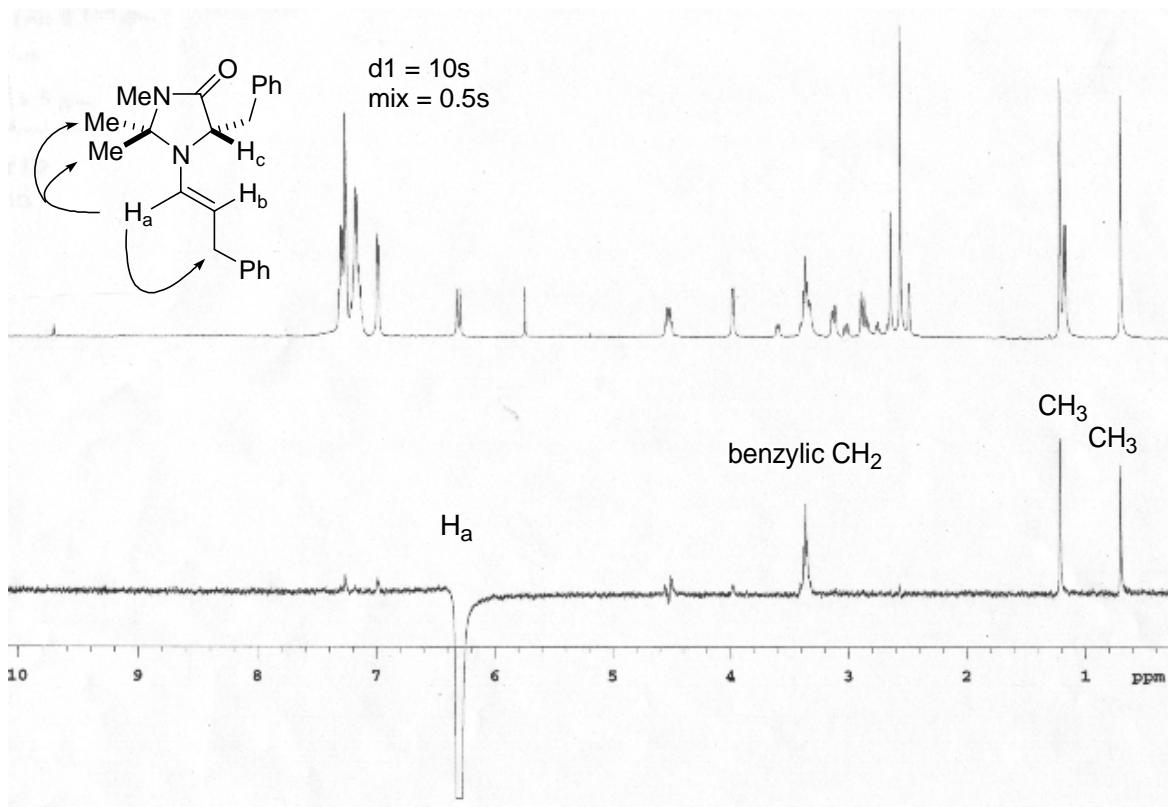


Preparation of Enamine 6: To 389 mg (1.78 mmol) of (*5S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (**1a**) in 5 mL of dry d6-DMSO⁸ was added 177 μ L (1.34 mmol) hydrocinnamaldehyde and 3g of freshly activated 4A MS⁹. The reaction was allowed to sit at room temperature without stirring for 1 week. ¹H NMR revealed complete conversion of the aldehyde to the desired enamine (the excess **1a** was also observed). ¹H NMR (300 MHz, D₆-DMSO) δ 7.10-7.34 (m, 8H), 6.98 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.31 (d, *J* = 14.1 Hz, 1H), 4.53 (dt, *J* = 14.1, 6.9 Hz, 1H), 3.99 (d, *J* = 3.9 Hz, 1H), 3.30-3.42 (m, 2H), 3.13 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.88 (dd, *J* = 13.2, 1.8 Hz, 1H), 2.57 (s, 3H), 1.23 (s, 3H), 0.70 (s, 3H).

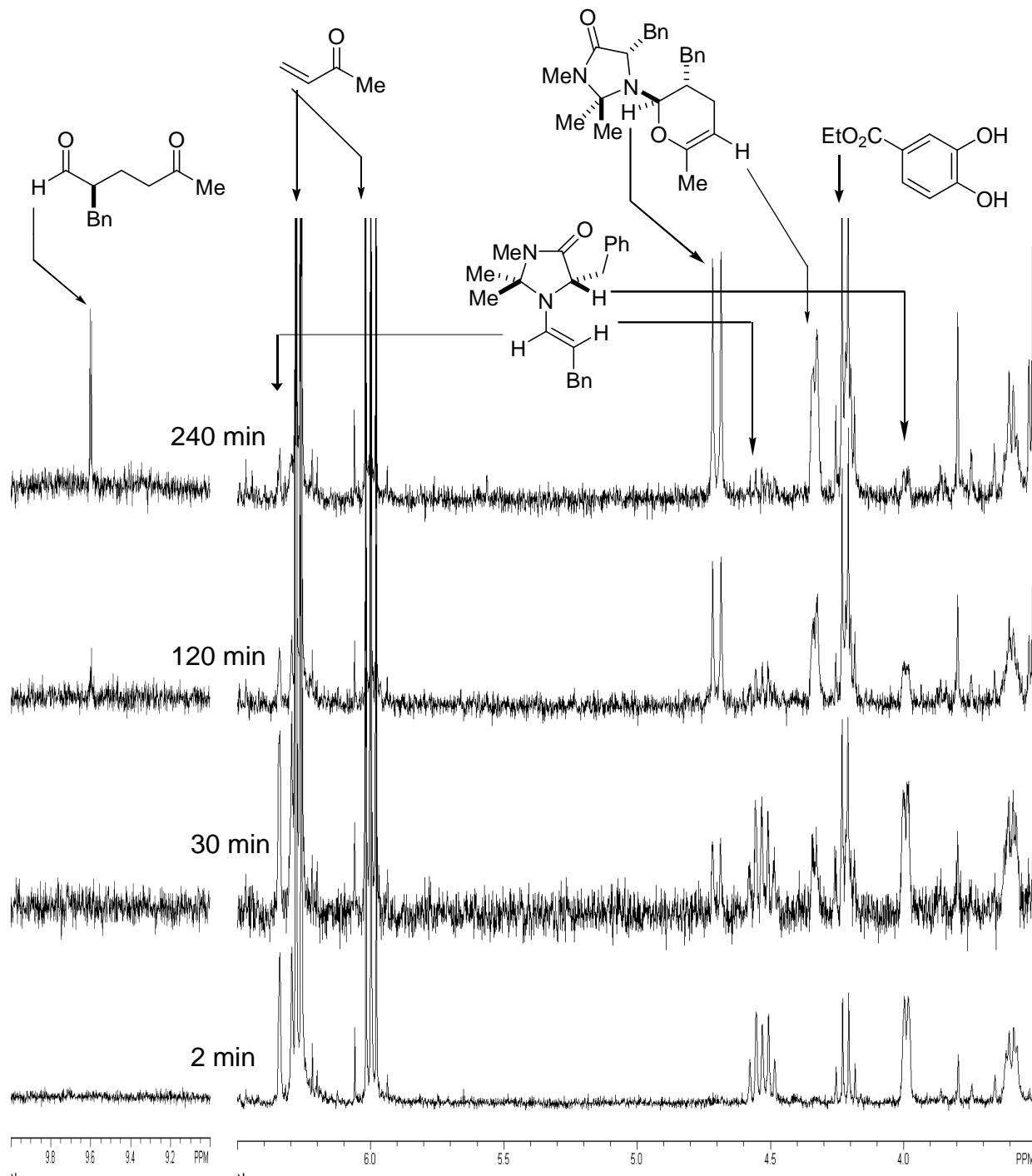
⁸ To ensure dryness, we used freshly opened 1 mL ampoules.

⁹ 4-8 mesh beads were used. Impurities were observed if ground 4A MS were used.

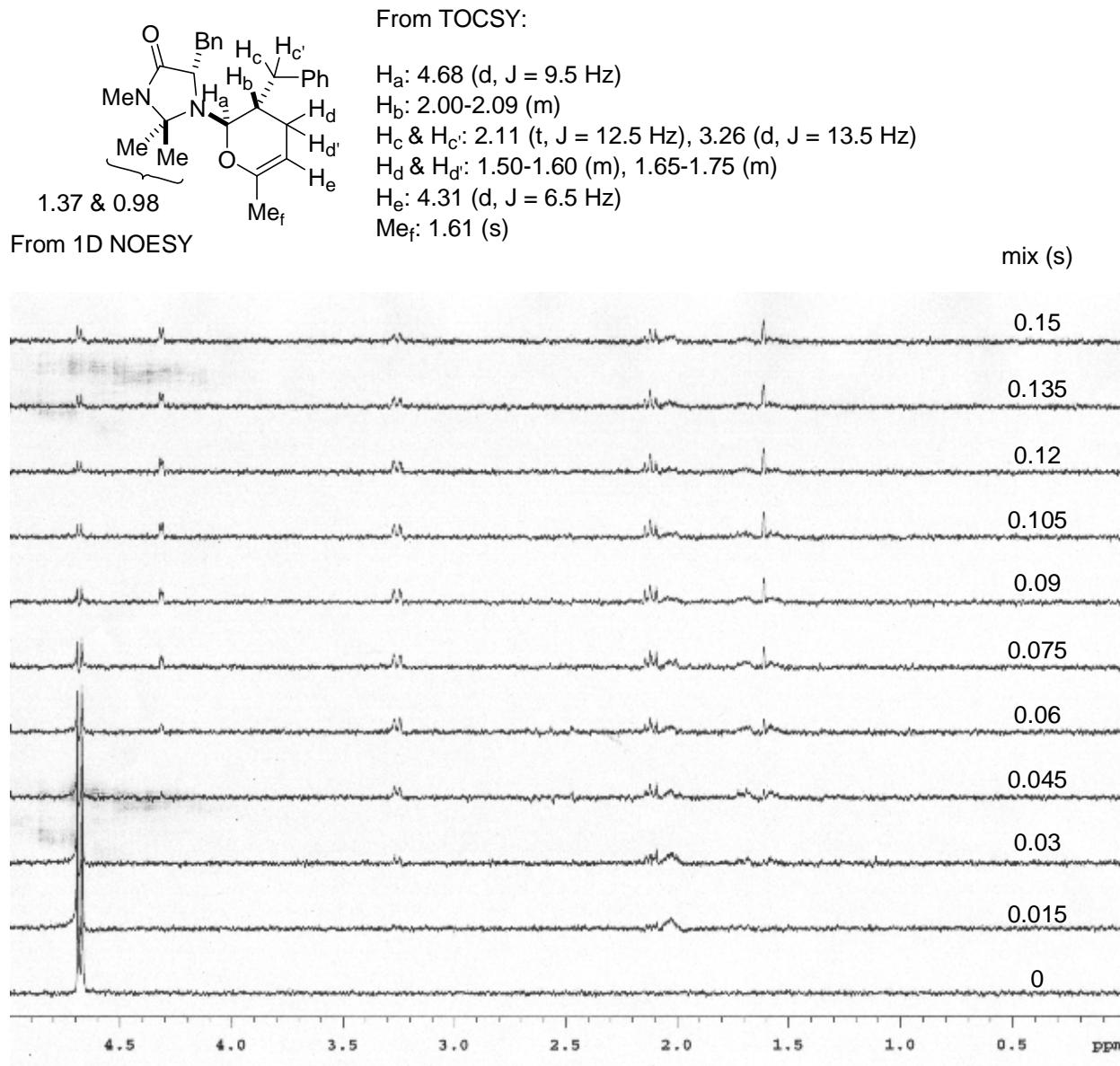




Reaction of enamine 6: Enamine **6** was prepared as described above and was concentrated by Kugelrohr distillation to generate approximately 0.25 mmol of neat enamine (along with additional imidazolidinone **1a**) as a colorless oil. To this oil was added 63 μ L of methyl vinyl ketone (0.75 mmol) and 9 mg of ethyl 3,4-dihydroxybenzoate (0.05 mmol). Aliquots were removed from the reaction periodically, dissolved in d6-DMSO, and immediately analyzed by ^1H NMR.



Assignment of structure and stereochemistry of dihydropyranone 8: Dihydropyranone **8** was assigned based on 1D NOESY and TOCSY experiments of the 240 min aliquot shown above. TOCSY experiments (irradiation of the doublet at 4.68 ppm) revealed gradual elaboration of a spin system consistent with the dihydropyran core. 1D NOESY experiments revealed contacts with two singlets consistent with the methyl groups attached to the imidizolidinone ring. The absolute chemistry at H_b is assigned according to the stereochemistry of the product. The H_a, H_b *trans* stereochemistry is assigned based upon the 9.5 Hz coupling constant, which is very close to the coupling constant ($J = 8.8$ Hz) observed in a similar *trans* dihydropyranone¹⁰, and far from the 2.6-3.0 Hz coupling constants observed in similar *cis* dihydropyranones.¹¹



¹⁰ Birkofe, L.; Quittmann, W. *Chem. Ber.* **1986**, *119*, 257.

¹¹ Shibata, Y.; Kosuge, Y.; Ogawa, S. *Carbohydr. Res.* **1990**, *199*, 37. Gallagher, T. F.; Horton, D. *Carbohydr. Res.* **1983**, *116*, 227.

