# Supporting Information

# Kinetic Modeling of the Nickel-Catalyzed Esterification of Amides

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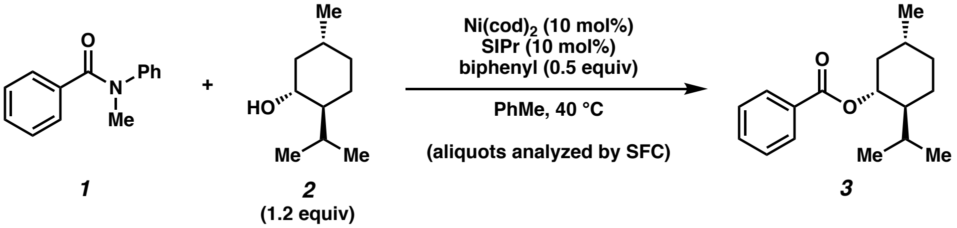
Supporting Information – Table of Contents

**Materials and Methods**. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen or argon and commercially obtained reagents were used as received. Non-commercially available substrates were synthesized following known protocols: **1**,[1a] **SI-1**,[1b] **SI-2**,[1c] **SI-3**.[1d] Prior to use, toluene was purified by distillation and taken through five freeze-pump-thaw cycles and alcohols were either purified by distillation or recrystallization. Ni(cod)$_2$ and SIPr (CAS No. 258278-28-3) were obtained from Strem Chemicals and stored in a glove box. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm for analytical chromatography and 0.50 mm for preparative chromatography) and visualized using a combination of UV, iodine, anisaldehyde, and potassium permanganate staining techniques. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. $^1$H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to residual solvent signals. Analysis of reaction mixtures in Section A in the Experimental Procedures was carried out on a Mettler Toledo SFC (supercritical fluid chromatography) with a Daicel ChiralPak OD-H column using 10% $CH_3CN$ as the polar cosolvent and 226 nm as the wavelength of observation.

## Experimental Procedures

### A. Development and Verification of the Kinetic Model

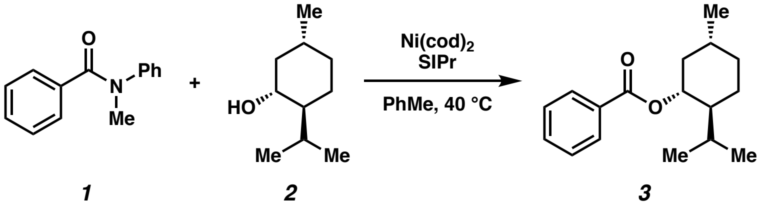


**Representative Procedure (coupling of amide 1 and (–)-menthol (2) is used as an example). Ester 3.** A 1-dram vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under $N_2$. Amide substrate **1** (211 mg, 1.00 mmol, 1.0 equiv), (–)-menthol (**2**, 187 mg, 1.20 mmol, 1.2 equiv), and biphenyl[2] (77.0, 0.500 mmol, 0.5 equiv) were added, and the vial was flushed with $N_2$. The vial was taken into a glove box and charged with $Ni(cod)_2$ (27.5 mg, 0.100 mmol, 10 mol%) and SIPr (39.1 mg, 0.100 mmol, 10 mol%). Subsequently, toluene (1.0 mL, 0.66 M)[3] was added. The vial was sealed with a Teflon-lined septum cap and stirred at 40 °C in the glove box. Periodically, aliquots of the homogeneous reaction mixture (approximately 50 μL each) were removed via syringe, placed into a 25 mL volumetric flask, and diluted to the mark with HPLC grade $CH_3CN$. Reaction conversion was then determined by SFC analysis with biphenyl as an internal standard. Typically, 4–6 aliquots were analyzed per reaction. The data was then plotted graphically and rate information was derived using *DynoChem*.[4]

*Any modifications of the conditions shown in the representative procedure above are specified below in Tables S1, S2, and S3.*

A number of exploratory experiments were designed to scope the sensitivity of the observed reaction rate to the following parameters: (a) ligand to metal ratio, (b) equivalents of (–)-menthol (**2**), (c) presence of product / byproduct spikes, and (d) length of time holding the catalyst at a given temperature prior to substrate addition (Table S1). No significant impact on the reaction rate was observed from changes to any of these variables.

**Table S1.** Summary of Exploratory Reaction Conditions

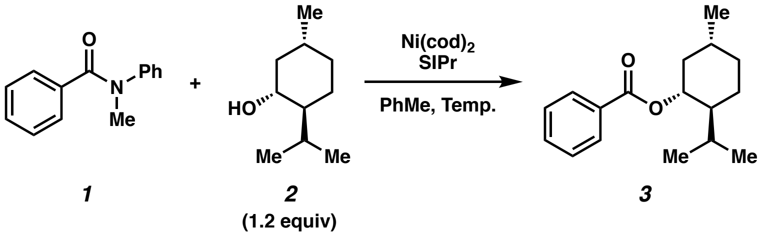


| Entry | Data Source | $Ni(cod)_2$ | $SIPr:Ni(cod)_2$ ratio | (–)-Menthol (equiv) | MePhNH spike (equiv) | Product spike (equiv) |
|---|---|---|---|---|---|---|
| 1 | NAW-5-043 | 10 mol% | 1:1 | 1.2 | 0.50 | – |
| 2 | NAW-5-044 | 10 mol% | 1:1 | 1.2 | – | 0.50 |
| 3[a] | NAW-5-045 | 10 mol% | 1:1 | 1.2 | – | – |
| 4[b] | NAW-5-046 | 10 mol% | 1:1 | 1.2 | – | – |
| 5 | NAW-5-047 | 5 mol% | 2:1 | 1.2 | – | – |
| 6 | NAW-5-052 | 10 mol% | 1:2 | 1.2 | – | – |
| 7 | NAW-5-058 | 10 mol% | 1:1 | 1.8 | – | – |

[a] Catalyst, ligand, alcohol, and toluene were held at 40 °C for 36 min before addition of substrate. [b] Catalyst, ligand, alcohol, and toluene were held at 40 °C for 654 min before addition of substrate.

The following reaction parameters were then selected for further evaluation: (a) temperature, (b) catalyst loading, and (c) reaction concentration. A handful of experiments were then used to train the model, varying temperatures as well as the amount of catalyst (Table S2). As expected, changes to these variables had a marked impact on the reaction kinetics.

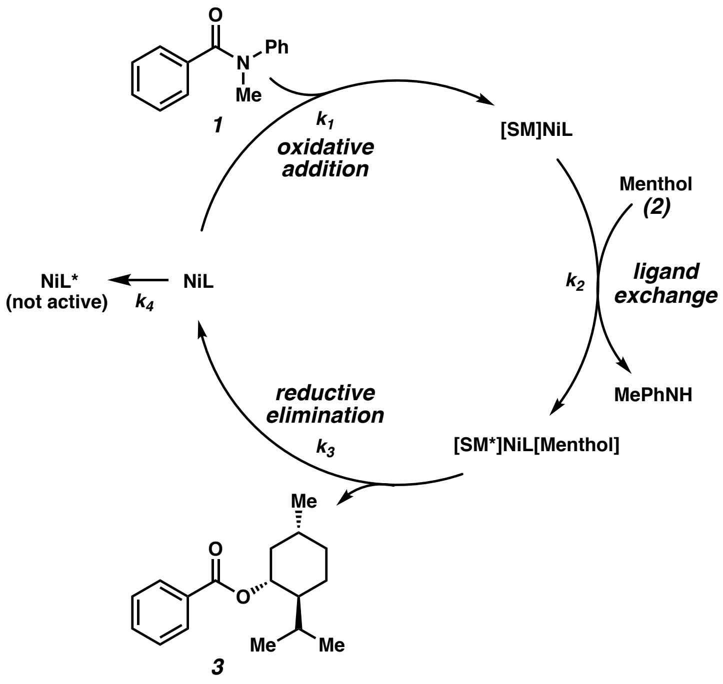
**Table S2.** Summary of Experiments Used to Train the Model



| Entry | Data Source | Ni(cod)$_2$ / SIPr | Temp. | Concentration[a] | Max Conversion | Time |
|---|---|---|---|---|---|---|
| 1 | NAW-5-042 | 10 mol% | 40 °C | 0.66 M | 92% | 8 h |
| 2 | NAW-5-061 | 10 mol% | 33 °C | 0.66 M | 70% | 6 h |
| 3 | NAW-5-060 | 10 mol% | 50 °C | 0.66 M | 91% | 4 h |
| 4 | NAW-5-073 | 0.5 mol% | 65 °C | 1.16 M | 77% | 8 h |
| 5 | NAW-5-069 | 0.1 mol% | 80 °C | 1.16 M | 13% | 1 h |

[a] Volume was approximated by summing the masses of all reactants, reagents, and solvent with an assumed overall density of 0.87 g/mL (toluene).

A simplistic reaction pathway was constructed using literature precedent as well as modeling work performed by the Houk laboratory on this transformation (Figure S1).[1d] Moreover, the obtained data was utilized to develop a kinetic model using *DynoChem* software. A review of the data in Table S2 also indicated the presence of a catalyst degradation pathway, as many reactions (in particular, entry 5) did not reach full conversion. The degradation kinetics ($k_4$) were represented by a simplified first-order pathway from the catalyst resting state (NiL). The regressed values and associated standard error of $k_1$ and $k_4$ are shown in Figure S1 below. The rate of ligand exchange ($k_2$) and reductive elimination ($k_3$) were not found to be rate-determining, and therefore an arbitrary fast rate was selected for fitting.



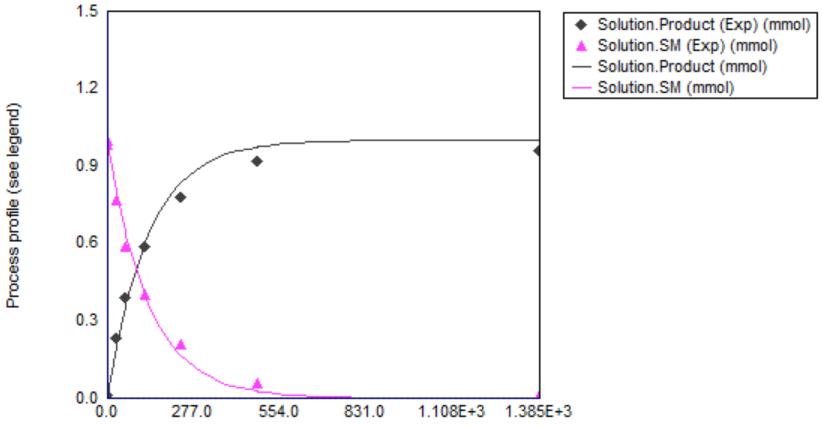
| Refined Forward Rate Constants (*k*)[a] | Activation Energy ($E_a$) (kJ/mol)[b] |
|---|---|
| $k_1 = (2.00 \pm 0.06) \times 10^{-3}$ L/mol•s | $E_{a1} = 97 \pm 2$ |
| $k_2 = 10$ L/mol•s[c] | $E_{a2} = 0$[d] |
| $k_3 = 10$ $s^{-1}$[c] | $E_{a3} = 0$[d] |
| $k_4 = (1.42 \pm 0.38) \times 10^{-6}$ $s^{-1}$ | $E_{a4} = 151 \pm 5$ |

[a] Rate constants are reported at 40 °C. The ± values represent the 95% confidence interval obtained from the *DynoChem* fitting of the data to the kinetic model. [b] For comparison, the corresponding values in kcal/mol are as follows: $E_{a1} = 23.0 \pm 0.5$ kcal/mol; $E_{a4} = 36.1 \pm 1.0$ kcal/mol. [c] This reaction is fast and not rate limiting, therefore an arbitrary fast rate of 10 was selected for subsequent fitting. [d] Reaction rate was a weak function of temperature within the explored temperature range.

**Figure S1.** Simplistic Reaction Pathway and Calculated Rate Constants

The experimentally observed time course data for each experiment in Table S2 was described accurately by the developed kinetic model described above (Figure S2).

**NW-5-042**



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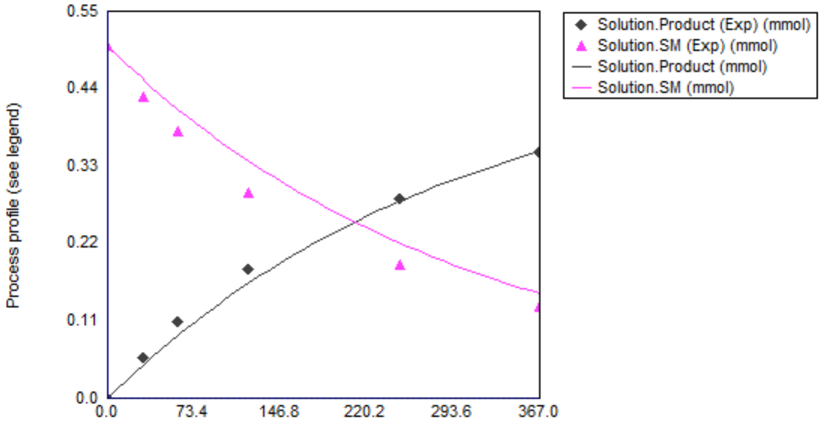

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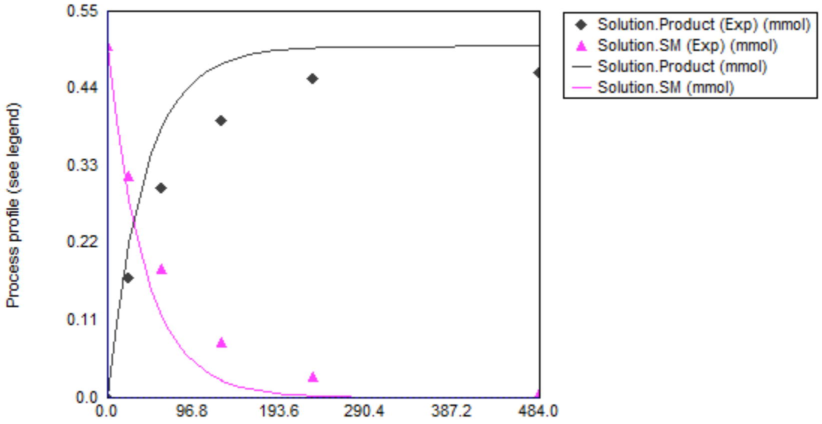


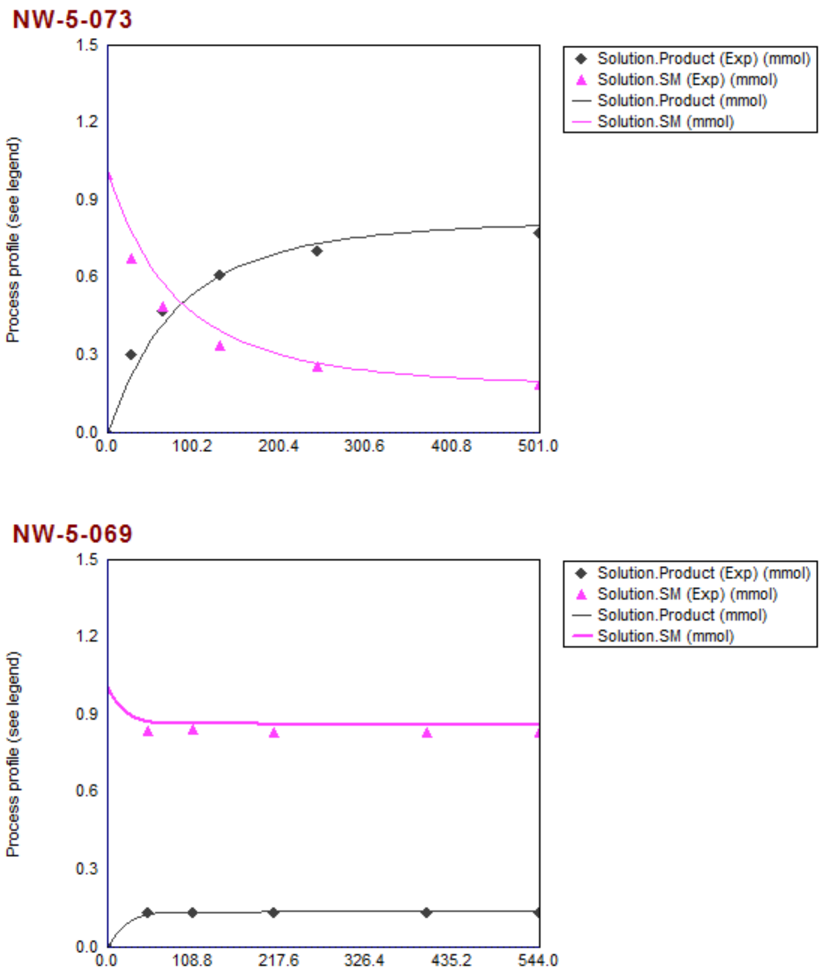
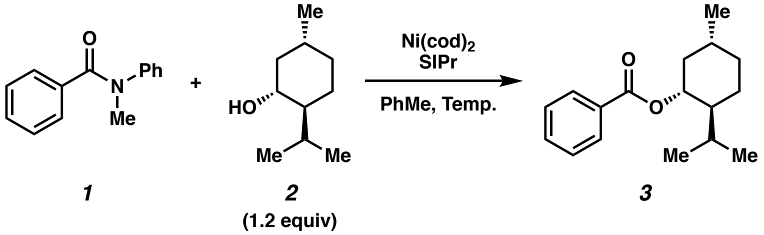


**Figure S2.** Concentration Profiles of Observed Values (Points) vs. Calculated Values (Curves);

x-axes: time (min); y-axes: mmol

Further independent experiments, which were not part of the training data set to estimate rate constants, were performed under atypical reaction conditions (Table S3). These experiments were used to verify the model prediction capabilities, with the model observed to have done a good job of predicting atypical reaction behavior (Figure S3).

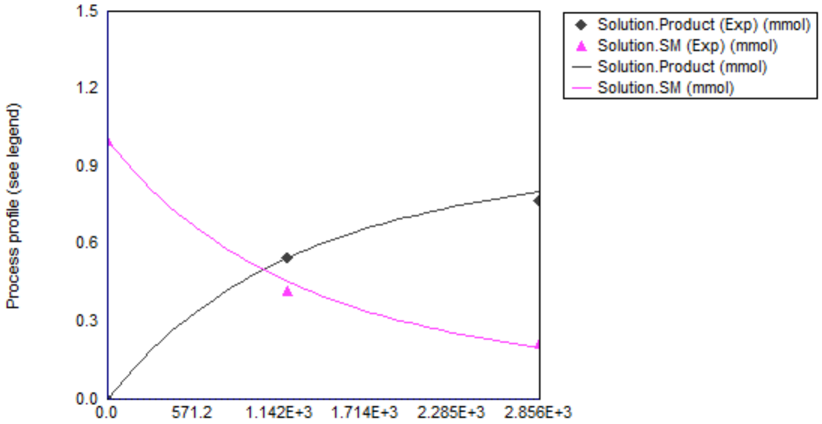
**Table S3.** Summary of Experiments Used to Verify the Model



| Entry | Data Source | Ni(cod)$_2$ | SIPr:Ni(cod)$_2$ ratio | Temp. | Concentration[a] | Max Conversion |
|---|---|---|---|---|---|---|
| 1 | NAW-5-111 | 0.2 mol% | 1:1 | 45 °C | 1.78 M | 77% |
| 2 | NAW-5-105 | 0.4 mol% | 1:1 | 45 °C | 1.51 M | 91% |
| 3 | NAW-5-114 | 0.4 mol% | 1:1 | 45 °C | 1.51 M | 76% |
| 4 | NAW-5-119 | 0.4 mol% | 2:1 | 45 °C | 1.51 M | 85% |
| 5 | NAW-5-124 | 0.4 mol% | 3:2 | 45 °C | 1.51 M | 77% |
| 6 | NAW-5-083 | 0.5 mol% | 1:1 | 45 °C | 1.16 M | 81% |
| 7 | NAW-5-102 | 0.6 mol% | 1:1 | 45 °C | 1.31 M | 94% |
| 8 | NAW-5-090[b] | 10 mol% | 1:1 | 50 °C | 0.66 M | 92% |
| 9 | NAW-5-080 | 1 mol% | 1:1 | 55 °C | 1.16 M | 94% |
| 10 | NAW-5-067 | 1 mol% | 1:1 | 60 °C | 1.04 M | 89% |
| 11 | NAW-5-072 | 0.1 mol% | 1:1 | 80 °C | 1.16 M | 14% |

[a] Volume was approximated by summing the masses of all reactants, reagents, and solvent with an assumed overall density of 0.87 g/mL (toluene). [b] Catalyst, ligand, alcohol, and toluene were held at 50 °C for 12.6 h before addition of substrate.

**NW-5-111**



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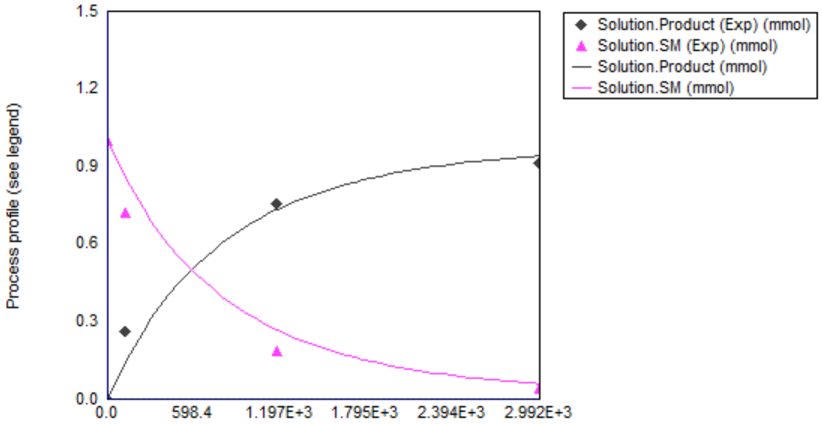

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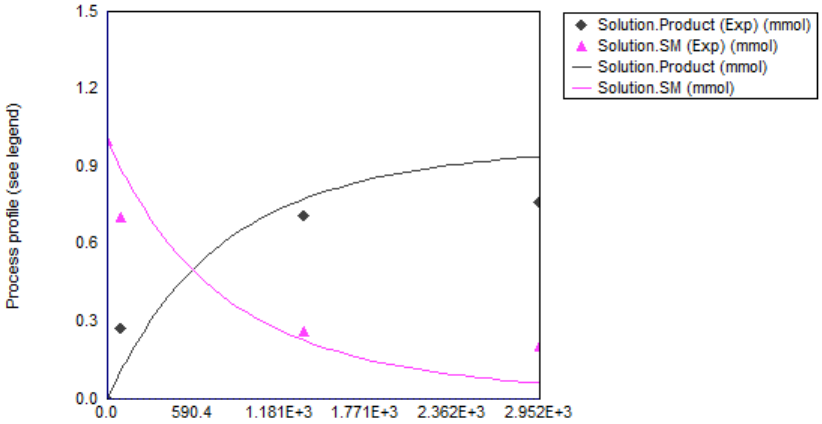

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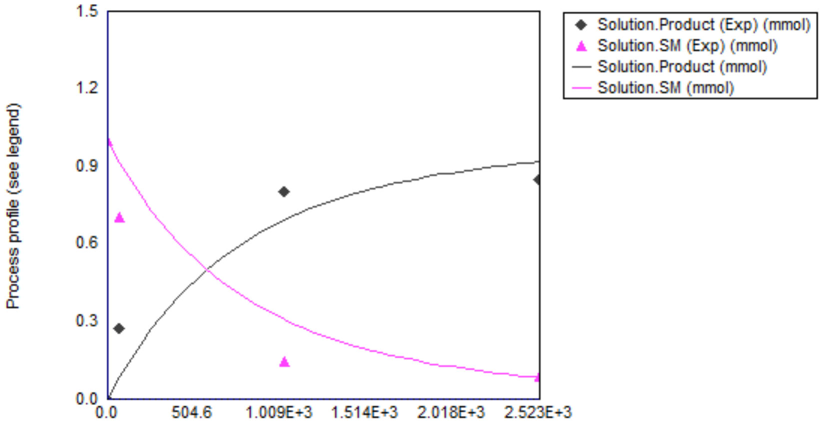

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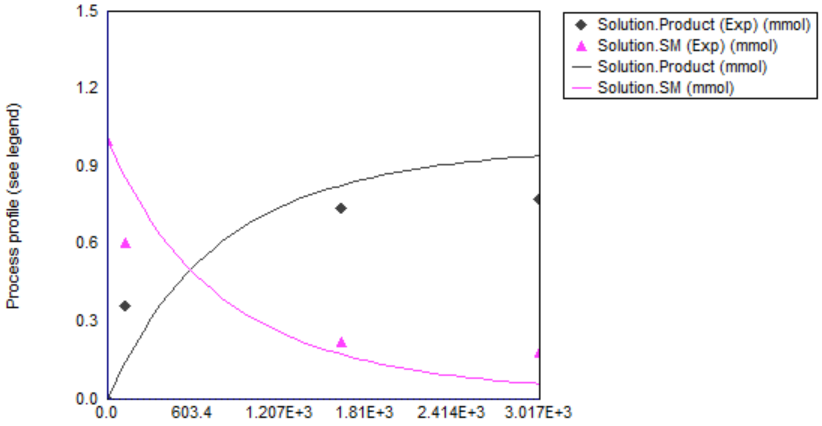
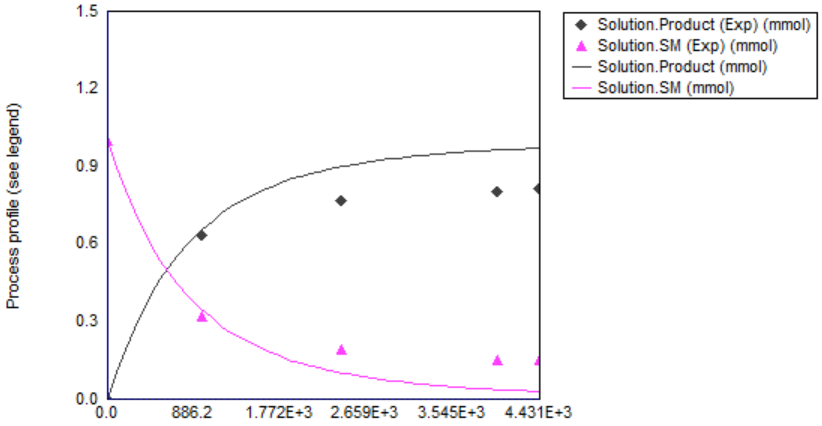
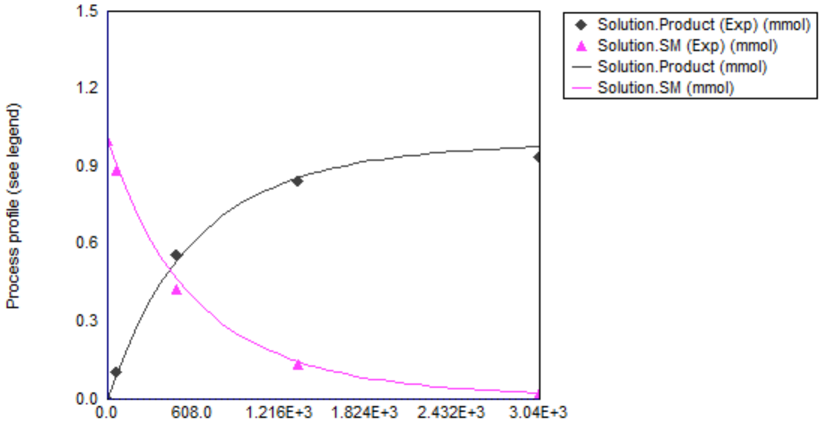


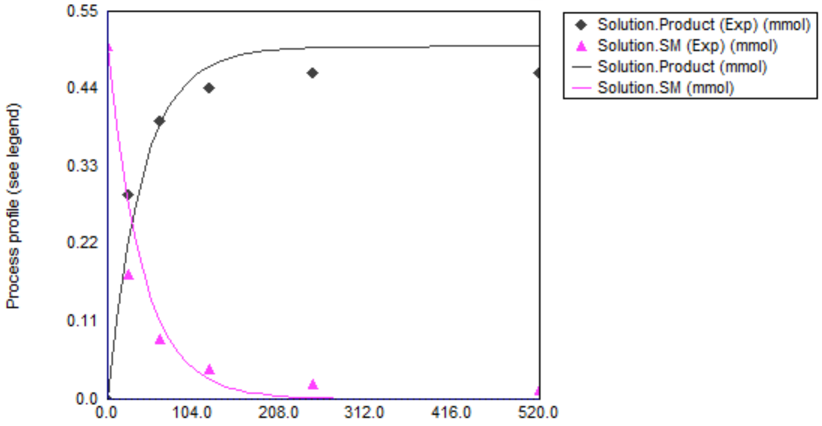
**NW-5-083**



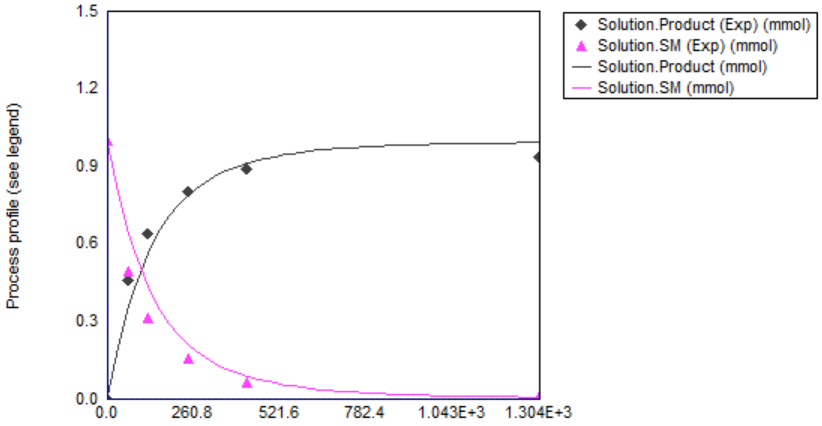
**NW-5-102**



**NW-5-090**



**NW-5-080**



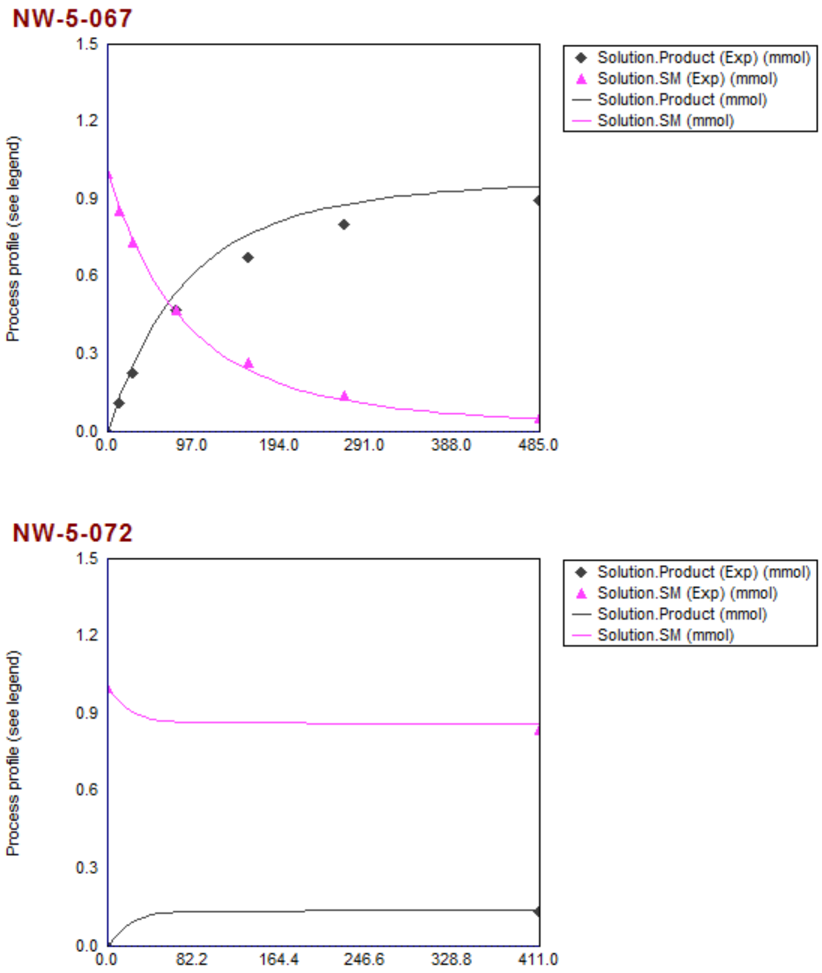


**Figure S3.** Concentration Profiles of Observed Values (Points) vs. Calculated Values (Curves);

x-axes: time (min); y-axes: mmol

With a working kinetic model in hand, thousands of *in silico* simulations were performed in minutes in order to visualize the multidimensional relationships between (a) reaction concentration, (b) reaction temperature, and (c) catalyst loading. These calculations were carried out with both catalyst loadings above and below 1.0 mol% (Figures S4 and S5).

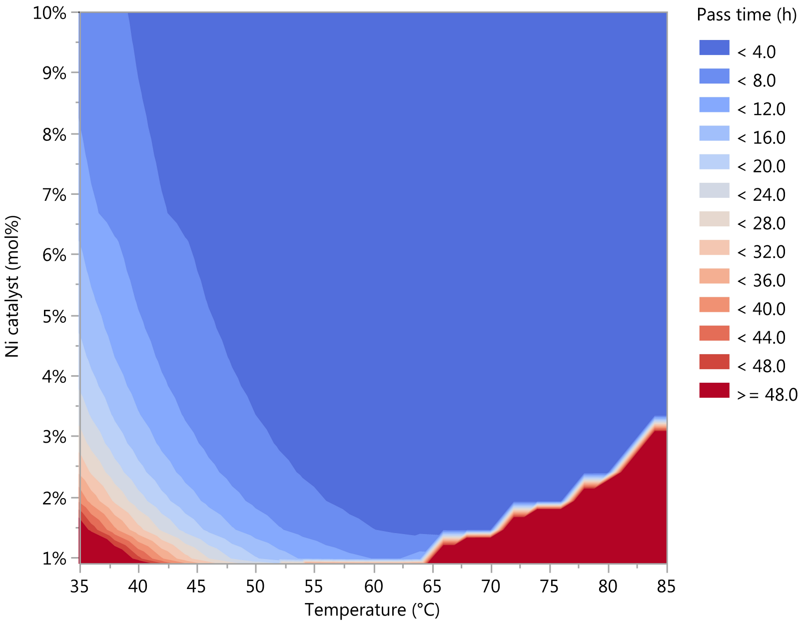


**Figure S4.** *In Silico* Simulations of Reaction Pass Time (95% Conversion) as a Function of Ni Catalyst (mol%) and Temperature for Overall Reaction Concentrations of 1.00–1.30 M.[3]

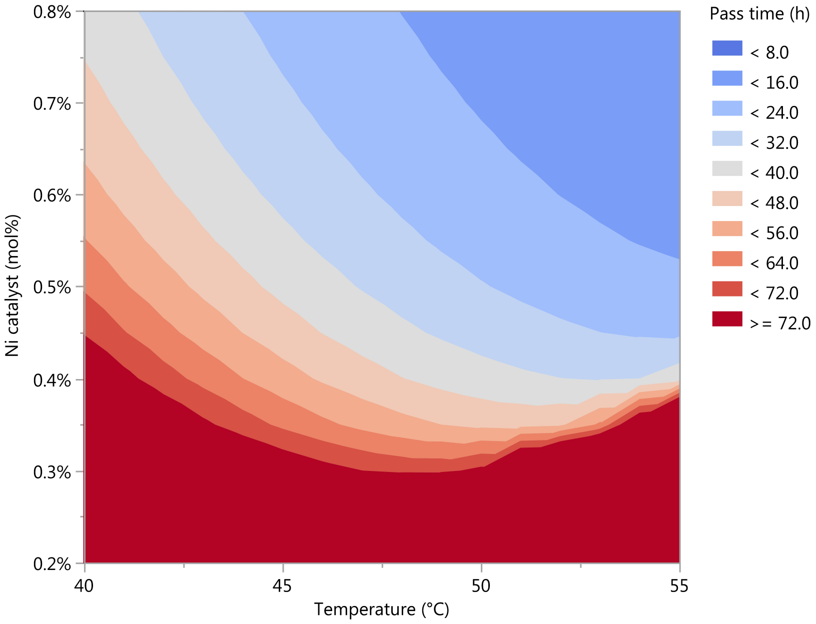
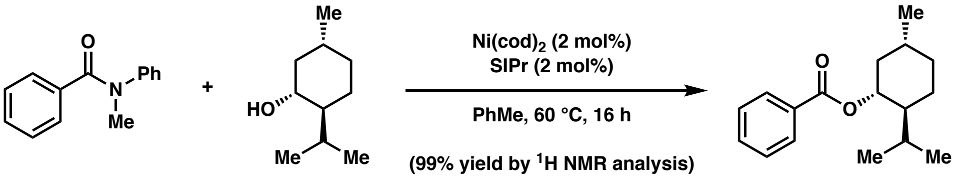


**Figure S5.** *In Silico* Simulations of Reaction Pass Time (95% Conversion) as a Function of Ni Catalyst (mol%) and Temperature for Overall Reaction Concentrations of 1.44–1.74 M.[3]

## B. Scope of Coupling Using 2 mol% Nickel



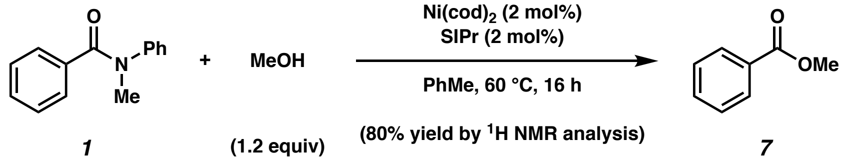
*1*

*2*
(1.2 equiv)

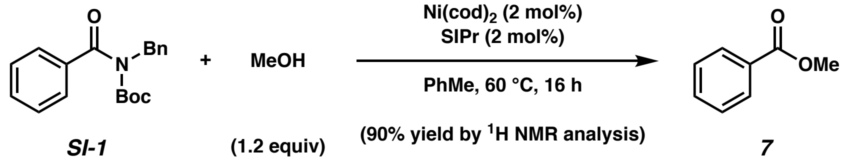
*3*

**Representative Procedure (coupling of amide 1 and (–)-menthol (2) is used as an example). Ester 3.** A 1-dram vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under $N_2$. Amide substrate **1** (106 mg, 0.500 mmol, 1.0 equiv) and (–)-menthol (**2**, 93.6 mg, 0.600 mmol, 1.2 equiv) were added, and the vial was flushed with $N_2$. The vial was taken into a glove box and charged with $Ni(cod)_2$ (2.8 mg, 0.010 mmol, 2 mol%) and SIPr (3.9 mg, 0.010 mmol, 2 mol%). Subsequently, toluene (0.25 mL, 1.04 M)[3] was added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 60 °C for 16 h. After cooling to 23 °C, the mixture was diluted with hexanes (0.5 mL) and filtered over a plug of silica gel (10 mL EtOAc eluent). The volatiles were removed under reduced pressure, and the yield was determined by $^{1}H$ NMR analysis with hexamethylbenzene as an external standard. Purification by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) generated ester **3** as a white solid. Ester **3**: $R_f$ 0.68 (5:1 Hexanes:EtOAc). The reported literature yield is 88%.[1d] Spectral data match those previously reported.[5]

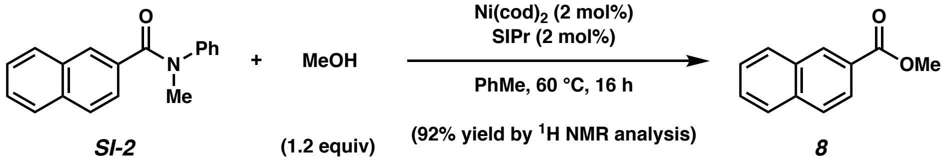
*Any modifications of the conditions shown in the representative procedure above are specified in the following schemes, which depict all of the results shown in Figure 5.*



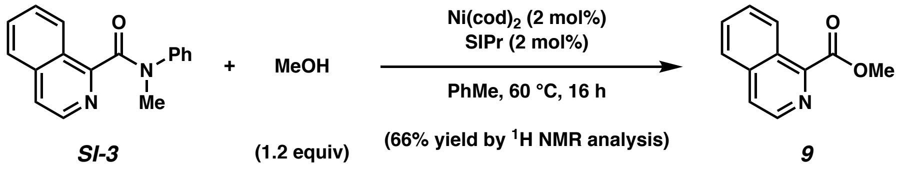
**Ester 7**. $^1$H NMR analysis of the crude reaction mixture indicated an 80% yield of ester **7** relative to hexamethylbenzene external standard. Purification by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) generated ester **7** as a clear oil. Ester **7**: R$_f$ 0.52 (5:1 Hexanes:EtOAc). The reported literature yield is 88%.[1d] Spectral data match those previously reported.[6]



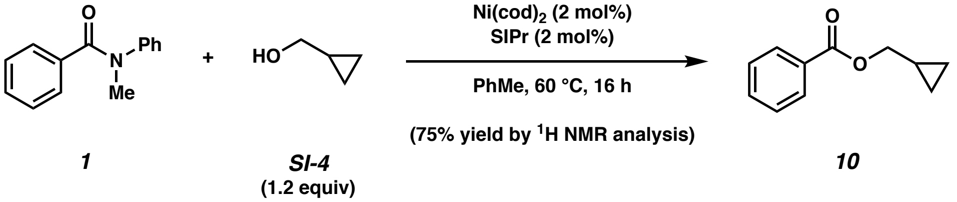
**Ester 7**. $^1$H NMR analysis of the crude reaction mixture indicated a 90% yield of ester **7** relative to hexamethylbenzene external standard. Purification by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) generated ester **7** as a clear oil. Ester **7**: R$_f$ 0.52 (5:1 Hexanes:EtOAc). The reported literature yield is 89%.[1d] Spectral data match those previously reported.[6]



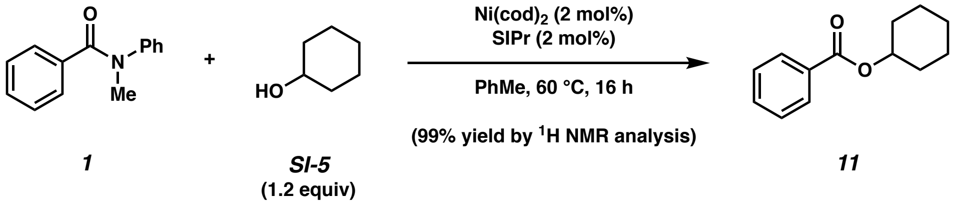
**Ester 8**. $^1$H NMR analysis of the crude reaction mixture indicated a 92% yield of ester **8** relative to hexamethylbenzene external standard. Purification by preparative thin-layer chromatography (100% PhH) generated ester **8** as a white solid. Ester **8**: R$_f$ 0.50 (5:1 Hexanes:EtOAc). The reported literature yield is 94%.[1d] Spectral data match those previously reported.[7]



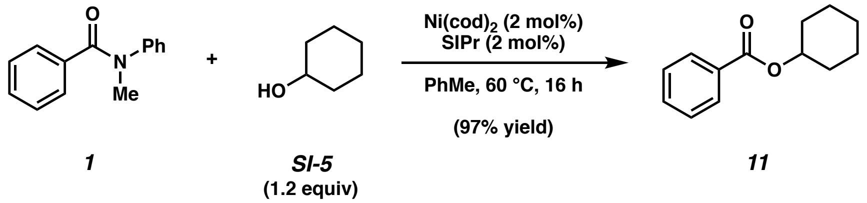
**Ester 9**. $^1$H NMR analysis of the crude reaction mixture indicated a 66% yield of ester **9** relative to hexamethylbenzene external standard. Purification by preparative thin-layer chromatography (1:1 Hexanes:EtOAc) generated ester **9** as a clear oil. Ester **9**: $R_f$ 0.30 (2:1 Hexanes:EtOAc). The reported literature yield is 56%.[1d] Spectral data match those previously reported.[8]



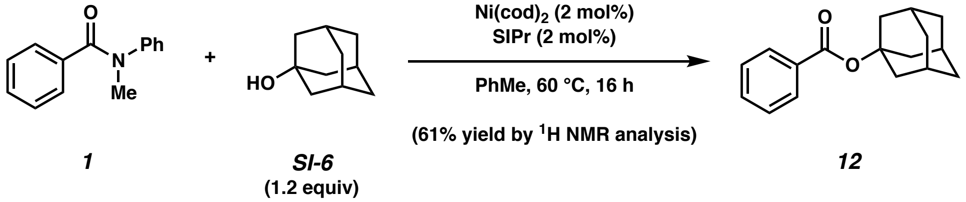
**Ester 10**. $^1$H NMR analysis of the crude reaction mixture indicated a 75% yield of ester **10** relative to hexamethylbenzene external standard. Purification by flash chromatography (49:1 Hexanes:EtOAc) generated ester **10** as a clear oil. Ester **10**: $R_f$ 0.65 (5:1 Hexanes:EtOAc). The reported literature yield is 90%.[1d] Spectral data match those previously reported.[1d]



**Ester 11**. $^1$H NMR analysis of the crude reaction mixture indicated a 99% yield of ester **11** relative to hexamethylbenzene external standard. Purification by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) generated ester **11** as a clear oil. Ester **11**: $R_f$ 0.56 (5:1 Hexanes:EtOAc). The reported literature yield is 82%.[1d] Spectral data match those previously reported.[9]

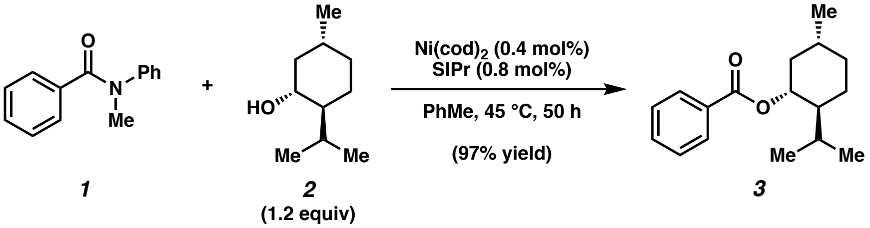


**Ester 11**. Purification by flash chromatography (49:1 Hexanes:EtOAc) generated ester **11** (99.3 mg, 97% yield) as a clear oil. Ester **11**: R*f* 0.56 (5:1 Hexanes:EtOAc). The reported literature yield is 82%.[1d] Spectral data match those previously reported.[9]



**Ester 12**. $^1$H NMR analysis of the crude reaction mixture indicated a 61% yield of ester **12** relative to hexamethylbenzene external standard. Purification by preparative thin-layer chromatography (5:1 Hexanes:EtOAc) generated ester **12** as a white solid. Ester **12**: R*f* 0.64 (5:1 Hexanes:EtOAc). The reported literature yield is 67%.[1d] Spectral data match those previously reported.[10]

## C. Multigram Scale Coupling Using 0.4 mol% Nickel



**Ester 3.** A 20 mL scintillation vial containing a magnetic stir bar was flame-dried under reduced pressure, and then allowed to cool under $N_2$. Amide substrate **1** (5.00 g, 23.7 mmol, 1.0 equiv) and (–)-menthol (**2**, 4.44 g, 28.4 mmol, 1.2 equiv) were added, and the vial was flushed with $N_2$. The vial was taken into a glove box and charged with Ni(cod)$_2$ (26.0 mg, 0.0947 mmol, 0.4 mol%) and SIPr (74.1 mg, 0.190 mmol, 0.8 mol%). Subsequently, toluene (4.74 mL, 1.52 M)[3] was added. The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and stirred at 45 °C for 50 h. After cooling to 23 °C, the mixture was diluted with hexanes (7 mL) and filtered over a plug of silica gel (500 mL EtOAc eluent). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography (99:1 Hexanes:EtOAc → 49:1 Hexanes:EtOAc → 24:1 Hexanes:EtOAc) to yield ester **3** (5.99 g, 97% yield) as a white solid. Ester **3**: $R_f$ 0.68 (5:1 Hexanes:EtOAc). The reported literature yield is 88%.[1d] Spectral data match those previously reported.[5]

## D. Complete List of Digital Object Identifiers (DOIs) Used to Compile Figure 1

SciFinder search for the research topic "nickel, cross-coupling" yielded hits corresponding to 83 original manuscripts in the journals *J. Am. Chem. Soc.*, *Angew. Chem. Int. Ed.*, *Science*, *Nature*, *Nat. Chem.*, and *Nat. Commun.* since 2015 (accessed 20 April, 2017). The manuscripts were then analyzed on an individual basis to determine the most frequently employed catalyst loading in each case. The following is a complete list of Digital Object Identifiers (DOIs) corresponding to sampled manuscripts used to compile Figure 1:

10.1002/anie.201409739

10.1002/anie.201410322

10.1002/anie.201410875

10.1002/anie.201500404

10.1002/anie.201502502

10.1002/anie.201502882

10.1002/anie.201503204

10.1002/anie.201503297

10.1002/anie.201503936

10.1002/anie.201504963

10.1002/anie.201505136

10.1002/anie.201505699

10.1002/anie.201506147

10.1002/anie.201507494

10.1002/anie.201509444

10.1002/anie.201510497

10.1002/anie.201511438

10.1002/anie.201601206

10.1002/anie.201601351

10.1002/anie.201601914

10.1002/anie.201601991

10.1002/anie.201604406

10.1002/anie.201604429

10.1002/anie.201604696

10.1002/anie.201605162

10.1002/anie.201605463

10.1002/anie.201605593

10.1002/anie.201606458

10.1002/anie.201606529

10.1002/anie.201607856

10.1002/anie.201607959

10.1002/anie.201611720

10.1002/anie.201611819

10.1002/anie.201700097

10.1002/anie.201702402

10.1021/ja511913h

10.1021/ja512498u

10.1021/ja512946e

10.1021/ja513079r

10.1021/ja513166w

10.1021/jacs.5b00473

10.1021/jacs.5b01909

10.1021/jacs.5b02503

10.1021/jacs.5b02945

10.1021/jacs.5b03870

10.1021/jacs.5b04725

10.1021/jacs.5b06466

10.1021/jacs.5b10963

10.1021/jacs.5b11244

10.1021/jacs.5b13211

10.1021/jacs.6b00250

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10.1021/jacs.6b06862

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10.1021/jacs.6b08075

10.1021/jacs.6b08397

10.1021/jacs.6b08507

10.1021/jacs.6b11412

10.1021/jacs.6b11962

10.1021/jacs.7b00049

10.1021/jacs.7b01705

10.1021/jacs.7b02389

10.1021/jacs.7b02742

10.1021/jacs.7b03448

10.1038/nature14676

10.1038/nature14875

10.1038/nature19056

10.1038/nature22307

10.1038/nchem.2388

10.1038/nchem.2587

10.1038/nchem.2741

10.1038/ncomms11073

10.1038/ncomms11129

10.1038/ncomms11676

10.1038/ncomms12937

10.1038/ncomms8508

10.1038/ncomms9404

10.1126/science.aaf6123

10.1126/science.aaf6635

10.1126/science.aam7355

## References

[1] (a) Li, Y.; Jia, F.; Li, Z. *Chem. Eur. J.* **2013**, *19*, 82–86. (b) Johnson II, D. C.; Widlanski, T. S. *Tetrahedron Lett*. **2004**, *45*, 8483–8487. (c) Baroudi, A.; Alicea, J.; Flack, P.; Kirincich, J.; Alabugin, I. V. *J. Org. Chem.* **2011**, *76*, 1521–1537. (d) Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79–83.

[2] Biphenyl is not required for the coupling to take place and does not affect the reaction rate.

[3] Concentration was calculated by approximating volume as the sum of the masses of all reactants, reagents, and solvents with an assumed overall density of 0.87 g/mL (toluene). Experimentally measured densities for reaction mixtures ranged from 0.85–0.91 g/mL.

[4] DynoChem®, by Scale-up Systems, is a leading process development and scale-up software for scientists and engineers working in the pharmaceutical industry and interfaces directly with Microsoft Excel.

[5] Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett*. **2013**, *15*, 5370–5373.

[6] Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc*. **2013**, *135*, 15257–15262.

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[8] Dong, J.; Shi, X.-X.; Yan, J.-J.; Xing, J.; Xhang, Q.; Xiao, S. *Eur. J. Org. Chem*. **2010**, *36*, 6987–6992.

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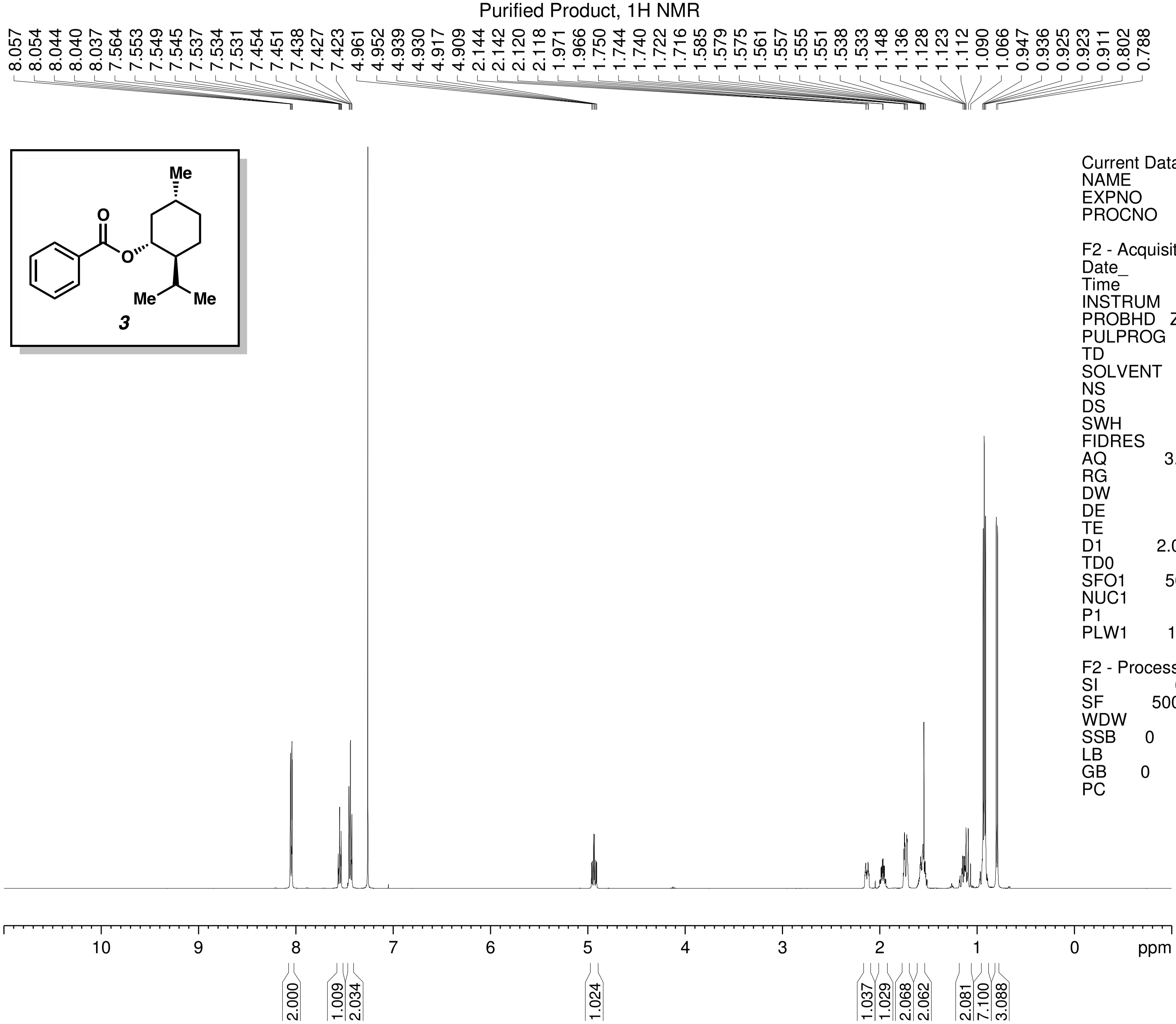
[10] Liu, Z.; Ma, Q.; Liu, Y.; Wang, Q. *Org. Lett*. **2014**, *16*, 236–239.

# $^{1}$H NMR Spectra



Purified Product, 1H NMR

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| PROCNO | 1 |

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| FIDRES | 0.305176 Hz |
| AQ | 3.2767999 sec |
| RG | 12.14 |
| DW | 50.000 usec |
| DE | 10.00 usec |
| TE | 298.0 K |
| D1 | 2.00000000 sec |
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| NUC1 | 1H |
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F2 - Processing parameters

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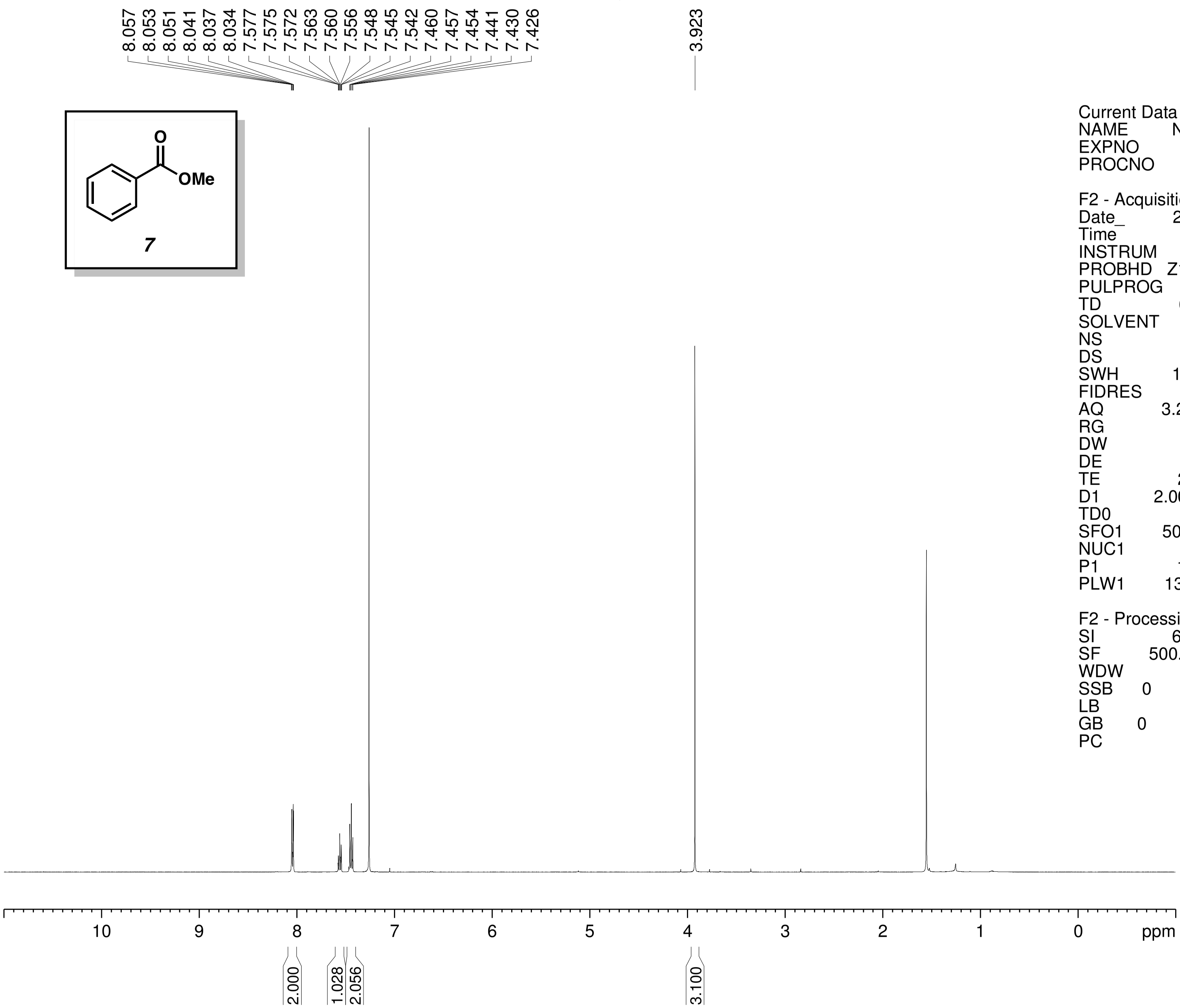
Purified Product, 1H NMR



7

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DS                  0
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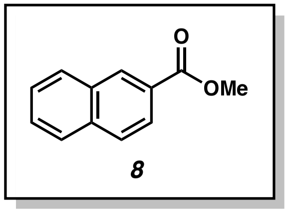
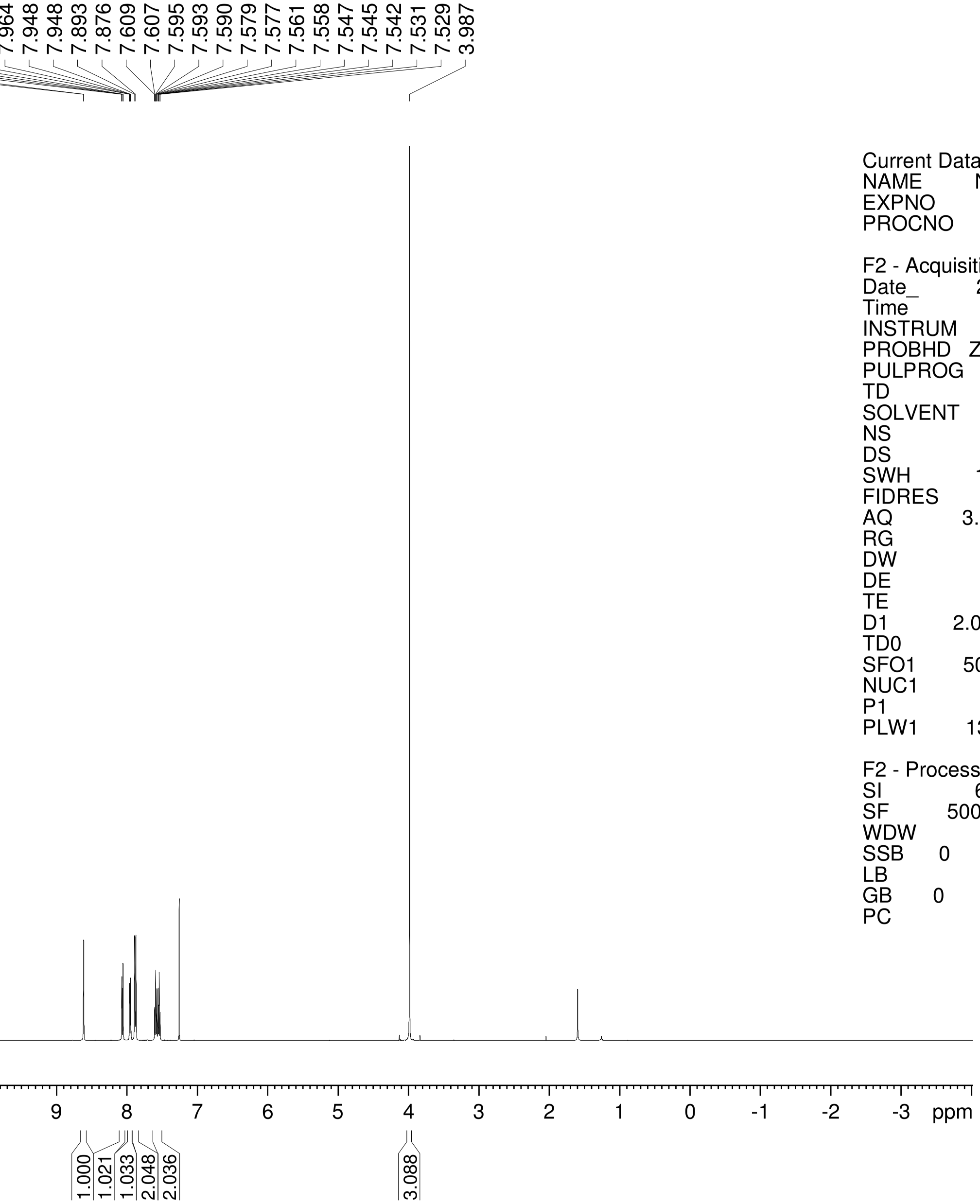
Purified Product, 1H NMR



*8*



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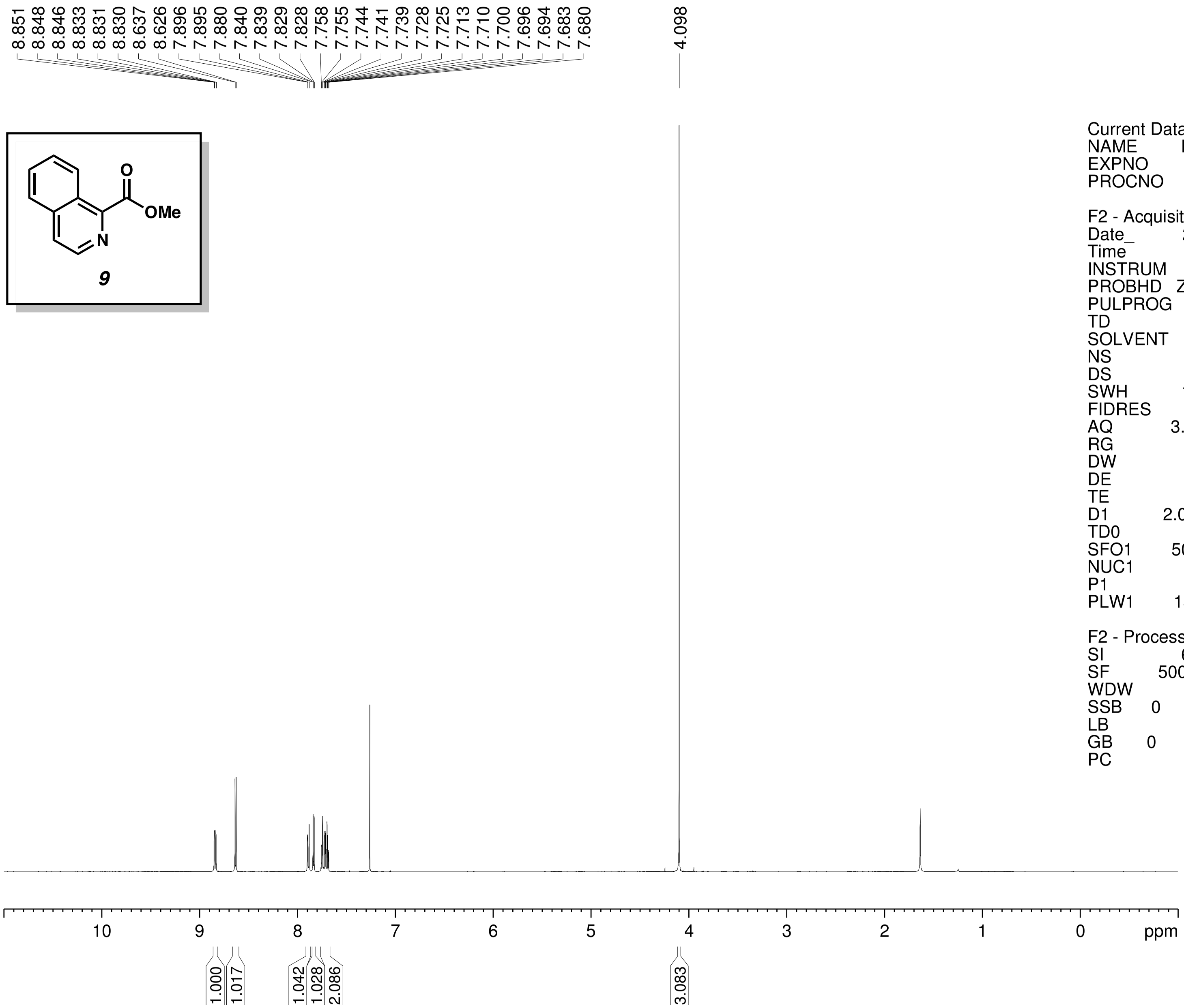
Purified Product, 1H NMR



**9**

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TE              298.0 K
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TD0                  1
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P1              10.00 usec
PLW1      13.50000000 W

F2 - Processing parameters
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PC              1.00
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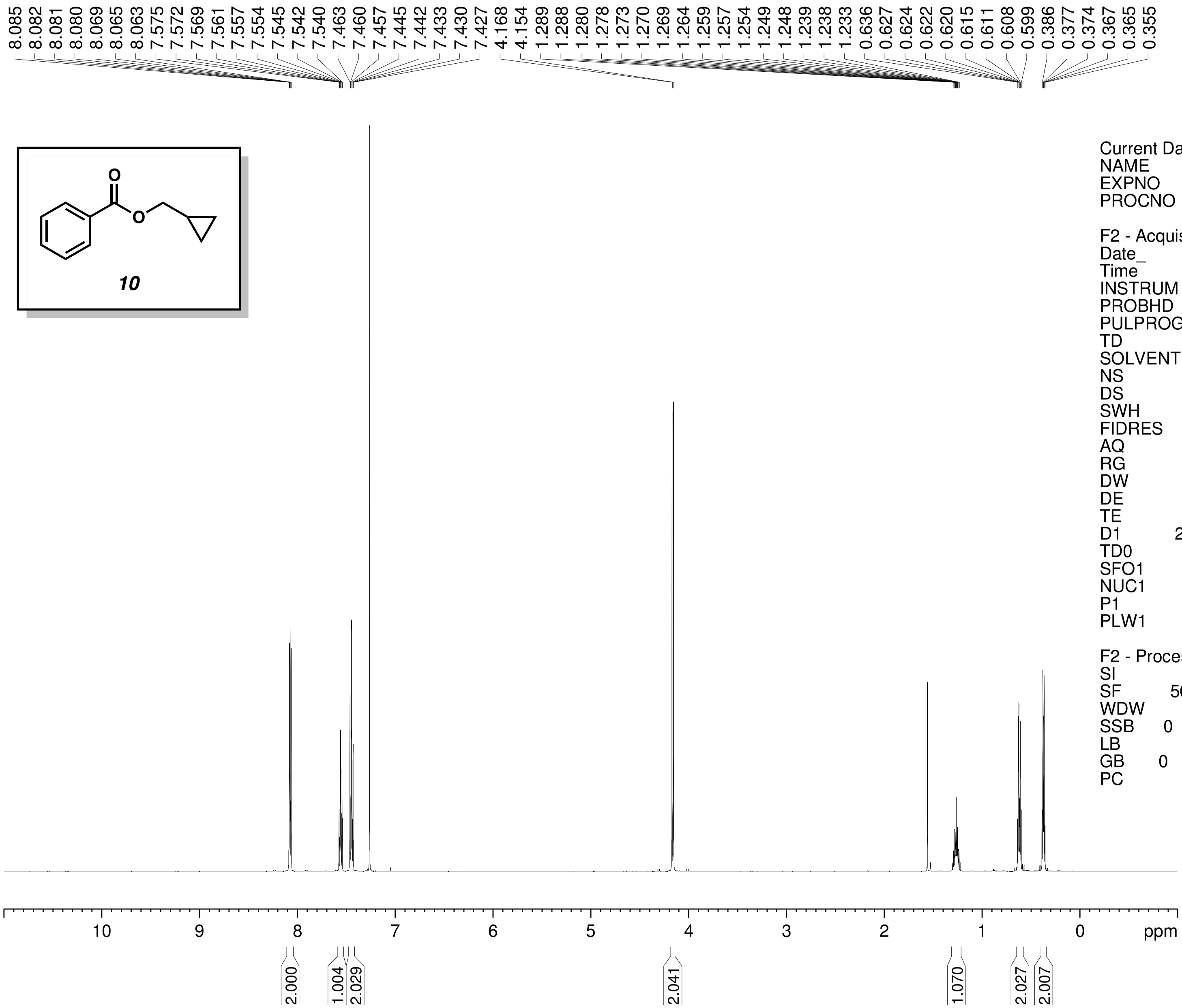
Purified Product, 1H NMR



**10**

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RG               12.14
DW              50.000 usec
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TE               298.0 K
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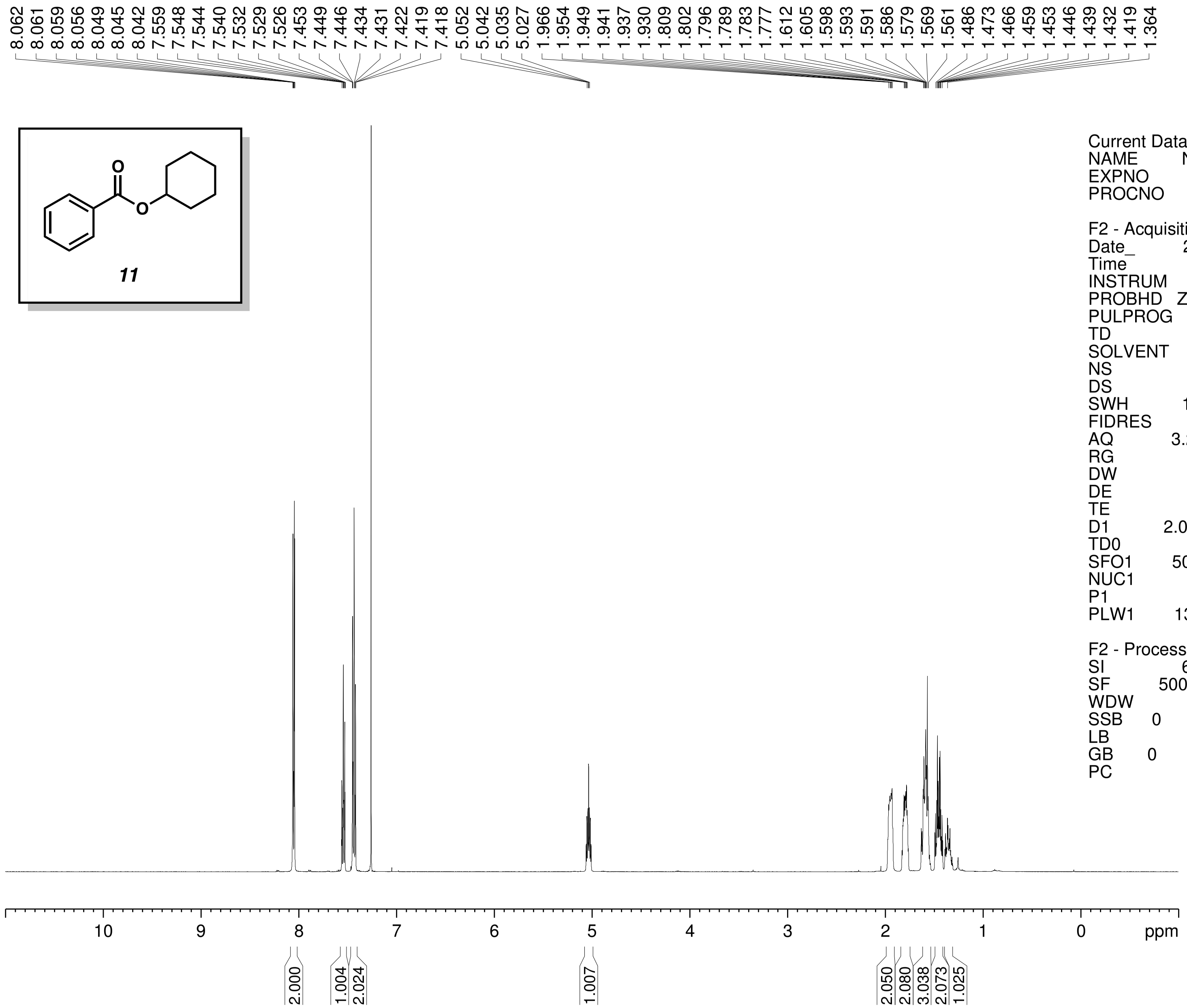

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FIDRES        0.305176 Hz
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RG                12.14
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   1
SFO1       500.1330008 MHz
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W

F2 - Processing parameters
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WDW                  EM
SSB      0
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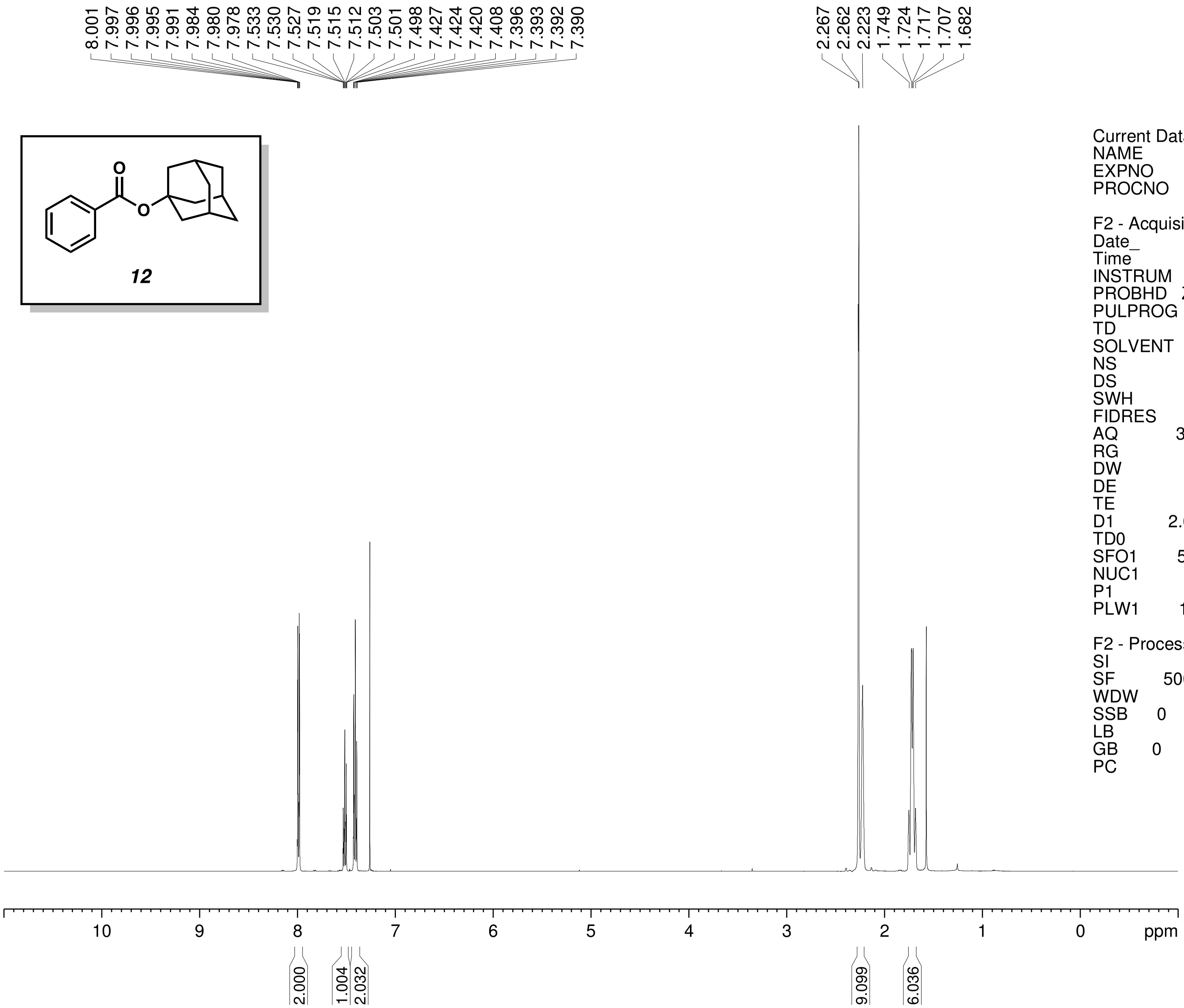
Purified Product, 1H NMR



**12**

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| P1 | 10.00 usec |
| PLW1 | 13.50000000 W |

F2 - Processing parameters

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