Electronic Supplementary Material (ESI) for Catalysis Science & Technology.

Supporting Information for:

Non-Directed Aromatic C-H Amination: Catalytic and Mechanistic Studies enabled by Pd Catalyst and Reagent Design

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Table of Contents

General Procedures

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 400 MHz NMR spectrometer with the residual solvent peak ($CDCl_3$: ^{1}H = 7.27 ppm, ^{13}C = 77.23 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ). Multiplicities are reported as follows: br (broad resonance), s (singlet), t (triplet), q (quartet), d (doublet), m (multiplet), app (apparent). Coupling constants (J) are reported in Hz. Infrared (IR) spectroscopy was performed on a Perkin Elmer FTIR. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100 %), m (medium, 40-67 %), w (weak, 20-40 %), and br (broad). High resolution mass spectroscopy was performed at the University of Notre Dame mass spectroscopy facility using a Q-Tof-2 mass spectrometer operating in positive ion mode.

Stock solutions were prepared using volumetric glassware and all liquid reagents were dispensed by difference using gas-tight Hamilton syringes. Ligands 1,2,3,4,5,6,7,8-octahydroacridine (**8**),[1] 1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (**6**),[2] and 1,1,3,3,6,6,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydroacridine (**9**)[3] were prepared according to literature procedures. Electrophilic amination reagents were

[1] Pilato, M. L.; Catalano, V. J.; Bell, T. W. Synthesis of 1,2,3,4,5,6,7,8-octahydroacridine via condensation of cyclohexanone with formaldehyde. *J. Org. Chem*. **2001**, *66* (4), 1425–1527.

[2] Thummel, R. P.; Kohli, D. K. Preparation and properties of annelated pyridines. *J. Org. Chem*. **1977**, *42* (16), 2742–2747.

[3] Newkome, G. R.; Fishel, D. L.; Pyrolysis of Ketone N,N,N-trimethylhydrazonium fluoroborates. III. Preparation of fused-ring pyridine. *J. Het. Chem*. **1967**, *4* (3), 427–430.

either synthesized according to literature procedures [4,5,6,7] or independently by new procedures described below.

AcOH[D_4] for H/D exchange experiments was purchased from Cambridge Isotopes Lab. H/D exchange data for benzene was measured on an Agilent GC-MS Q5000 using a xTi®-5 (serial # 790776) column obtained from Agilent. All raw data were deconvoluted using Periana's benzene H/D exchange worksheet with a reported error of 5%.[8] An assumption in the worksheet is that the fragmentation pattern of each isotopolog is identical. To obtain the most accurate analysis, pure samples of each isotopolog must be analyzed to determine the exact coefficients of the polynomial expansion for the given instrument. This treatment confirmed that the calculated percents of each isotopolog were within the reported error of the worksheet. All solvents ued were dried over activated molecular sieves prior to use.

[4] Cai, Xiong, et al. Multi-functional small molecules as anti-proliferative agents., U.S. Patent Application 11/852,458.

[5] Jones, L. W., Neuffer, L. "Hydroxamic acids related α-hydroxy acids and to acrylic acid, and a study of their rearrangements, *J. Am. Chem. Soc., **1917**, 39* (4), *659–668*

[6] Guimond, N., Gorelsky, S. I., Fagnou, K. Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies, *J. Am. Chem. Soc.,* **2011**, *133* (16), 6449–6457

[7] Middleton, W. J., Trifluoroacetonitrile oxide. *J. Org. Chem., **1984**, 49* (5)*, 919–922*

[8] Young, K. H. J.; Meier, S. K.; Gonzales, J. M.; Oxgaard, J.; Goddard III, W. A; Periana, R. A. *Organometallics* **2006**, *25*, 4734-4737.

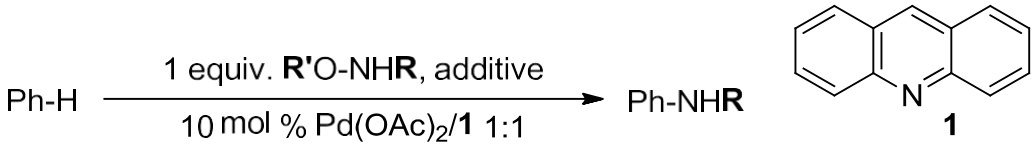
Initial Optimization of C-H Amination with Acridine (1) as Ligand

To a scintillation vial (5 mL) was added benzene (0.50 mL, 5.6 mmol, 40 equiv), palladium acetate (3.1 mg, 14 μmol, 10 mol %), **1** (2.5 mg, 14 μmol, 10 mol %) and the corresponding amination reagents (140 μmol, 1.0 equiv). The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. The reaction was allowed to cool to room temperature.

Product Analysis by NMR (for synthesis of PhNHAc): 0.50 mL (corresponding to 5.0 mg; 29 μmol of 1,3-dinitrobenzene) of a standard solution containing NMR solvent and 1,3-dinitrobenzene as NMR standard (50 mg; 290 μmol in 5.0 mL of $CDCl_3$) were added to the mixture. The resulting solution was filtered through celite. The amount of product formed was determined by integration of the NMR signals at 8.97 ppm (1H, 1,3-dinitrobenzene) and 2.21 ppm (3H, PhNHC(O)$\underline{CH_3}$) (relaxation time = 15.0 s, NS = 16).

Product Analysis by GC (for synthesis of PhNHC(O)CF_3): 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL saturated, aqueous K_2CO_3 solution. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. The amount of product formed was determined by calibrated GC analysis.

Table 1. Calibrated GC Yields of C-H Amination Optimization with Acridine as Ligand. Conditions: benzene (0.50 mL, 5.6 mmol, 40 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), acridine (2.5 mg, 14 μmol, 10 mol %), amination reagent (140 μmol, 1.0 equiv), 100 °C, 24 hr.



Additive	R'O	R	Yield PhNHR
none	AcO	Ac	11 ± 2%
none	AcO	$C(O)CF_3$	21 ± 2%
none	AcO	Ts	13 ± 1%
none	TsO	Ts	10 ± 1%
none	F_3CCO_2	$C(O)CF_3$	22 ± 2%
0.6 eq AcOH	AcO	Ac	27 ± 2%
1.0 eq AcOH	AcO	Ac	29 ± 2%
1.3 eq AcOH	AcO	Ac	25 ± 2%
2.5 mol % AgOAc	AcO	Ac	19 ± 2%
5 mol % AgOAc	AcO	Ac	27 ± 1%
10 mol % AgOAc	AcO	Ac	20 ± 2%
2.5 mol % C_6F_5N	AcO	Ac	37 ± 2%
5 mol % C_6F_5N	AcO	Ac	41 ± 1%
10 mol % C_6F_5N	AcO	Ac	30 ± 2%
0.6 eq AcOH	F_3CCO_2	$C(O)CF_3$	23 ± 1%
1.0 eq AcOH	F_3CCO_2	$C(O)CF_3$	17 ± 1%
1.3 eq AcOH	F_3CCO_2	$C(O)CF_3$	16 ± 1%
2.5 mol % AgOAc	F_3CCO_2	$C(O)CF_3$	24 ± 2%
5 mol % AgOAc	F_3CCO_2	$C(O)CF_3$	22 ± 1%
10 mol % AgOAc	F_3CCO_2	$C(O)CF_3$	17 ± 1%
2.5 mol % C_6F_5N	F_3CCO_2	$C(O)CF_3$	22 ± 1%
5 mol % C_6F_5N	F_3CCO_2	$C(O)CF_3$	28 ± 2%
10 mol % C_6F_5N	F_3CCO_2	$C(O)CF_3$	17 ± 1%
No Pd catalyst	AcO	Ac	0%
$Pd(OPiv)_2$ instead of $Pd(OAc)_2$	AcO	Ac	8 ± 1%
$Pd(O_2CCF_3)_2$ instead of $Pd(OAc)_2$	AcO	Ac	7 ± 2%
PPh_3 instead of **A**	AcO	Ac	5 ± 2%
Pyridine (**5**) instead of **A**	AcO	Ac	7 ± 2%
$P(o\text{-}tol)_3$ instead of **A**	AcO	Ac	6 ± 1%

DFT Calculations

All calculations used DFT methodologies implemented in the Gaussian 09 program.[9] All the data presented here results from calculations which employed the B3LYP set of functionals.[10] For Pd, we applied the LANL2Dz basis set,[11] all other atoms(O,N,C and H) were assigned 6-311+G(2d,p) basis sets.[12] All geometries and potential energies were calculated by standard optimization procedures in acetic acid (AcOH as a solvent and T= 298 K, 25 ºC or 373 K, 100 ºC. Enthalpies (ΔH) and Gibbs' free energies (ΔG; T = 298.15 or 373 K, P = 1 atm) were subsequently obtained from the potential energies (ΔE) using standard thermodynamic corrections.[13]

[9] Frisch, M. J.; et al., Gaussian 09, revision C.01; Gaussian, Inc.:Wallingford, CT, 2009.

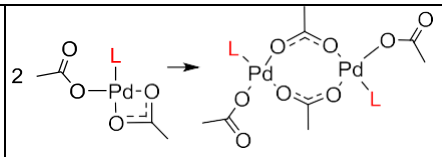
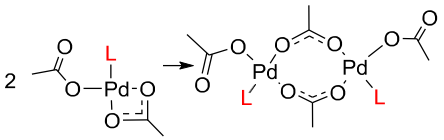
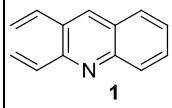
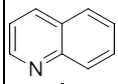
[10] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[11] Roy, L. E., Hay, P. J. & Martin, R. L. J. Chem. Theory Comput. 2008, 4, 1029-1031.

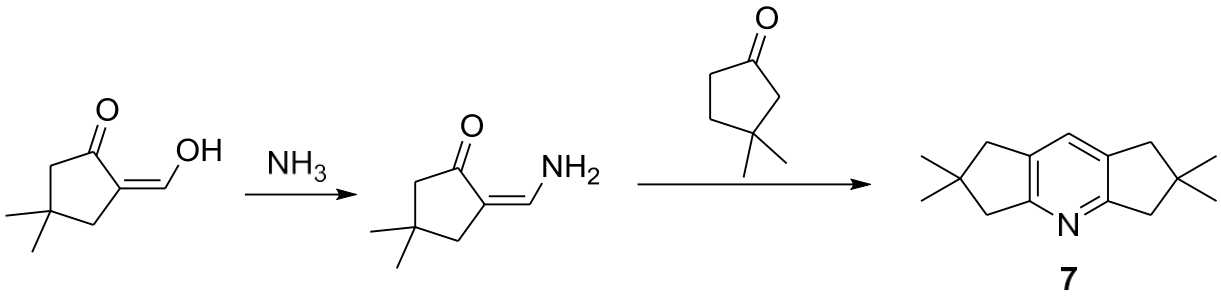
[12] Raghavachari, K.; Binkley, J. S.; Seeger, R.; Pople, J. A. J. Chem. Phys. 1980, 72, 650-654.

[13] McQuarrie, D. A. *Statistical Thermodynamics*; Harper and Row: New York, 1973.

Table 2. Energies and Enthalpies of Dimer Formation. All energy and enthalpy values are tabulated in kcal/mol; entropy values are tabulated in cal/(mol K). Thermodynamically favorable dimers (anti vs. syn) are bolded for each temperature.

									
Ligand L	***T (K)***	**ΔE_{anti}**	**ΔG_{anti}**	**ΔH_{anti}**	**ΔS_{anti}**	**ΔE_{syn}**	**ΔG_{syn}**	**ΔH_{syn}**	**ΔS_{syn}**
 1	*373*	-1.1	20.3	0.9	-52.1	-8.7	**+12.2**	-6.6	-50.3
	298	-1.1	16.4	0.6	-52.9	-8.7	**+8.4**	-6.8	-51.1
 4	*373*	-1.6	18.8	0.1	-50.2	-13.2	**+8.1**	-11.4	-52.2
	298	-1.6	15.0	-0.2	-50.9	-13.2	**+4.2**	-11.6	-53.0
 5	*373*	-19.5	**+0.7**	-17.5	-48.8	-17.2	4.4	-16.1	-54.9
	298	-19.5	**-3.0**	-17.8	-49.6	-17.2	0.3	-16.1	-55.2

Preparation of Ligand 7



7

The synthesis of **7** was executed in analogy to the previously described synthesis of **6**.[14]

Preparation of 2-(aminomethylene)-4,4-dimethylcyclopentan-1-one: A steady stream of ammonia gas was passed through a solution of 2-(hydroxymethylene)-4,4-dimethylcyclopentan-1-one (300 mg, 2.14 mmol, 1.00 eq.) in chloroform (3 mL) at 23 ºC for 30 min. The solution was allowed to stand at 23 ºC for 18 h, dried over $MgSO_4$ and filtered. After evaporation of the solvent, 2-(aminomethylene)-4,4-dimethylcyclopentan-1-one (280 mg, 2.00 mmol, 94%) was obtained as yellow solid. The crude product was used in the next step without further purification.

*Preparation of ligand **7***: A mixture of 2-(aminomethylene)-4,4-dimethylcyclopentan-1-one (280 mg, 2 mmol, 1.00 eq.), 3,3-dimethylcyclopentan-1-one (224 mg, 2 mmol, 1.00 eq.), ammonium acetate (245 mg, 5 mmol, 5.00 eq.), and acetic

[14] Thummel, R. P.; Kohli, D. K. Preparation and properties of annelated pyridines. *J. Org. Chem*. **1977**, *42* (16), 2742–2747.

acid (0.23 ml, 4.02 mmol, 2.00 eq.) was heated at 120 ºC for 72 h. After allowing the mixture to cool to room temperature, the residue was extracted with diethyl ether (5 x 10 mL). The organic layers were combined, the solvent was removed in vacuum, and the resulting residue was purified by column chromatography (silica, 1:9 hexanes:ethyl acetate) to obtain ligand **7** as a yellow solid (99 mg, 23%).

^{1}H NMR (400 Mz, $CDCl_3$, 25 ºC): δ = 7.20 (s, 1H; ArH), 2.78 (s, 4H; CH_2), 2.65 (s, 4H; CH_2), 1.16 ppm (s, 12H; CH_3);

^{13}C (NMR 100 Mz, $CDCl_3$, 25 ºC): δ = 162.6, 134.1, 129.5, 49.1, 45.8, 38.7, 29.3 ppm;

IR (KBr): $\tilde{\nu}$ = 2990 (s), 2841 (s), 2801 (m), 1701 (w), 1573 (m), 1516 (m), 1477 (s), 1450 (s), 1390 (m), 1287 (m), 1231 (m), 1201 (w), 1145 (m), 1099 (m), 971 (s), 883 (s), 790 (s), 770 (s), 733 (m) cm^{-1};

HRMS calc. 216.1752; found 216.1750 (M+H).

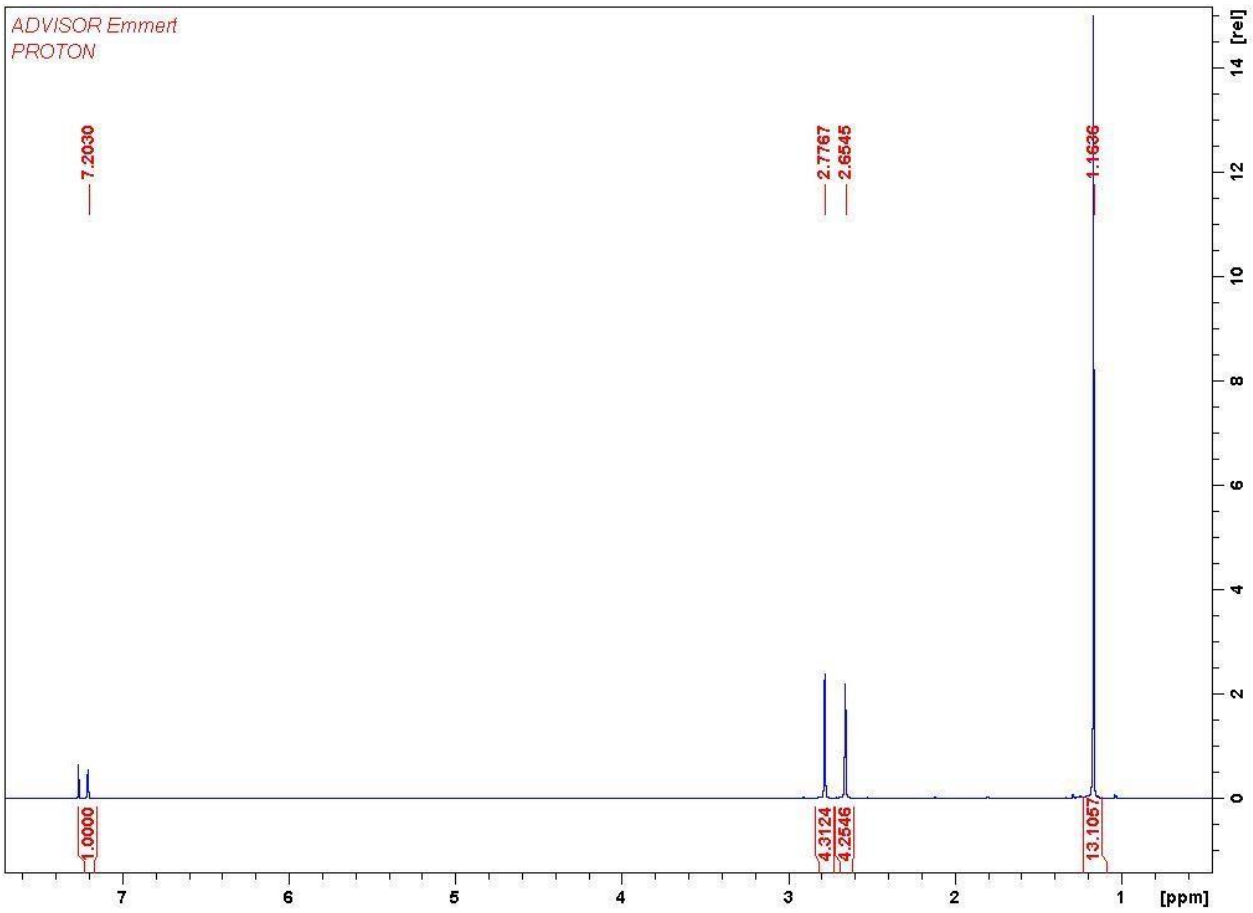


Figure 1. ^{1}H NMR spectrum of 7 in $CDCl_3$.

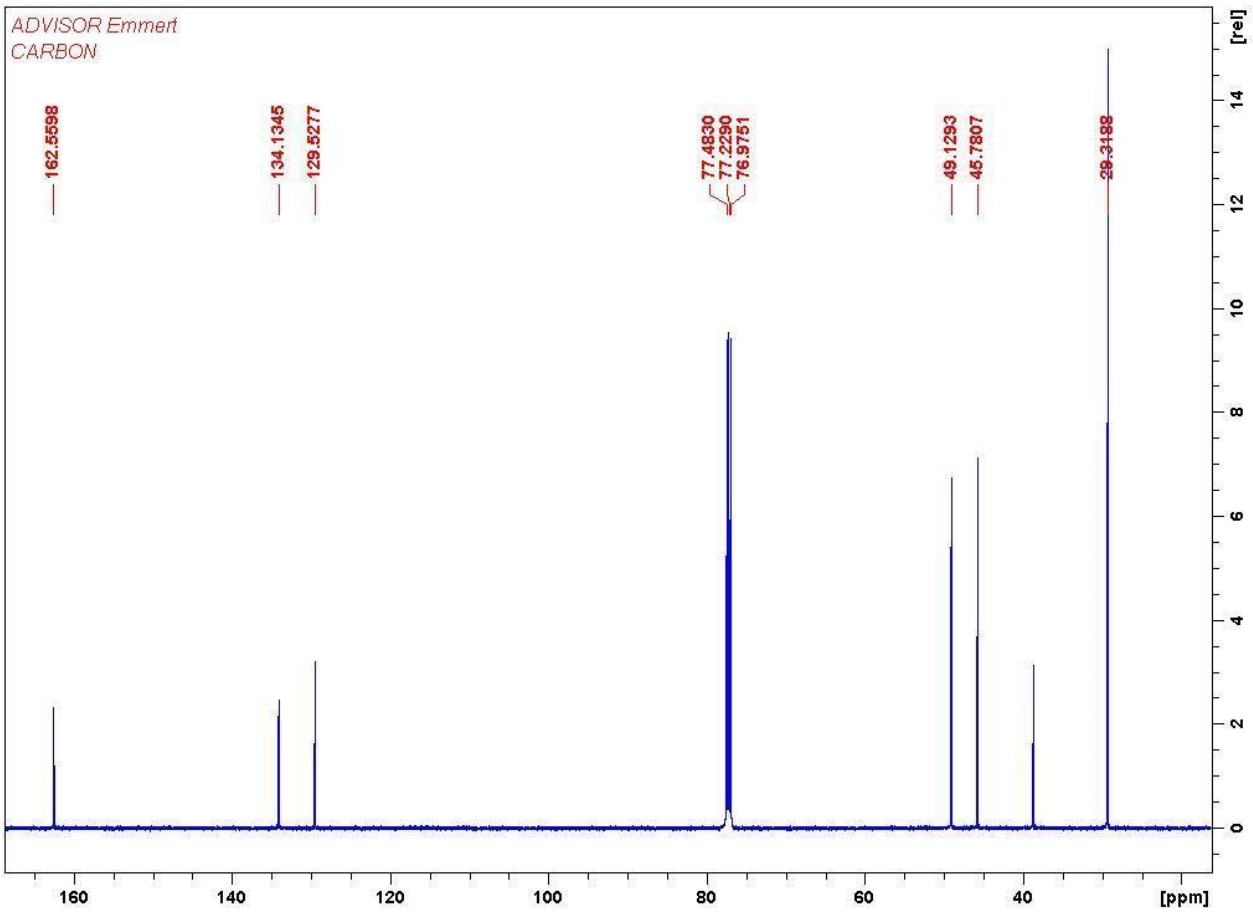
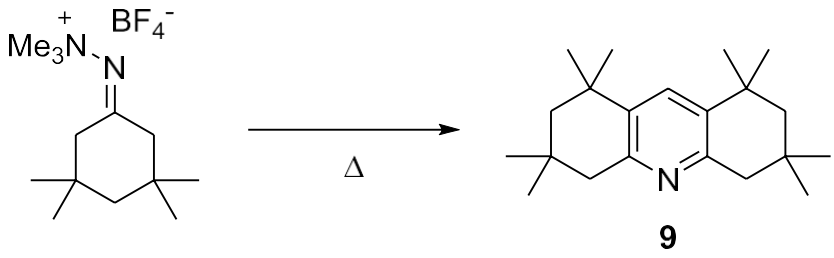


Figure 2. ^{13}C NMR spectrum of 7 in $CDCl_3$.

Preparation of Ligand 9



9

9 was obtained using a modified literature procedure.[15]

N,N,N-trimethyl-*N'*-3,3,5,5-tetramethylcyclohenehydrazone tetrafluoroborate (100 mg, 0.290 mmol, 1.00 eq) was placed in a placed in a 5 mL pressure tube and heated under nitrogen at 215 ºC for 18 h. After allowing to cool to room temperature, the residue was extracted with benzene (5 × 10 mL). The organic layers were combined, the solvent was removed in vacuum and the resulting residue was purified by column chromatography (silica, 1:10 hexanes:ethyl acetate) to obtain ligand **9** as a brown oil (23 mg, 23%) which solidified upon storing at 8 ºC.

^{1}H NMR (400 Mz, $CDCl_3$, 25 ºC): δ = 7.53 (s, 1H; ArH), 2.17 (s, 4H; CH_2), 1.59 (s, 4H; CH_2), 1.31 ppm (s, 12H; CH_3) 1.03 ppm (s, 12H; CH_3);

^{13}C (NMR 100 Mz, $CDCl_3$, 25 ºC): *δ* = 162.9, 136.7, 118.9, 41.9, 36.1, 31.5, 20.0, 14.2, 13.9 ppm;

[15] Newkome, G. R.; Fishel, D. L.; Pyrolysis of Ketone N,N,N-trimethylhydrazonium fluoroborates. III. Preparation of fused-ring pyridine. *J. Het. Chem*. **1967**, *4* (3), 427–430.

IR (KBr): $\tilde{\nu}$ = 3001 (s), 2941 (s), 2900 (s), 2833 (m), 1710 (w), 1577 (m), 1517 (m), 1457 (s), 1405 (s), 1389 (s), 1299 (s), 1220 (m), 1190 (w), 1109 (m), 1050 (m), 970 (s), 878 (s), 797 (s), 777 (s), 747 (m) cm^{-1};

HRMS calc. 302.3317; found 302.3315 (M+H).

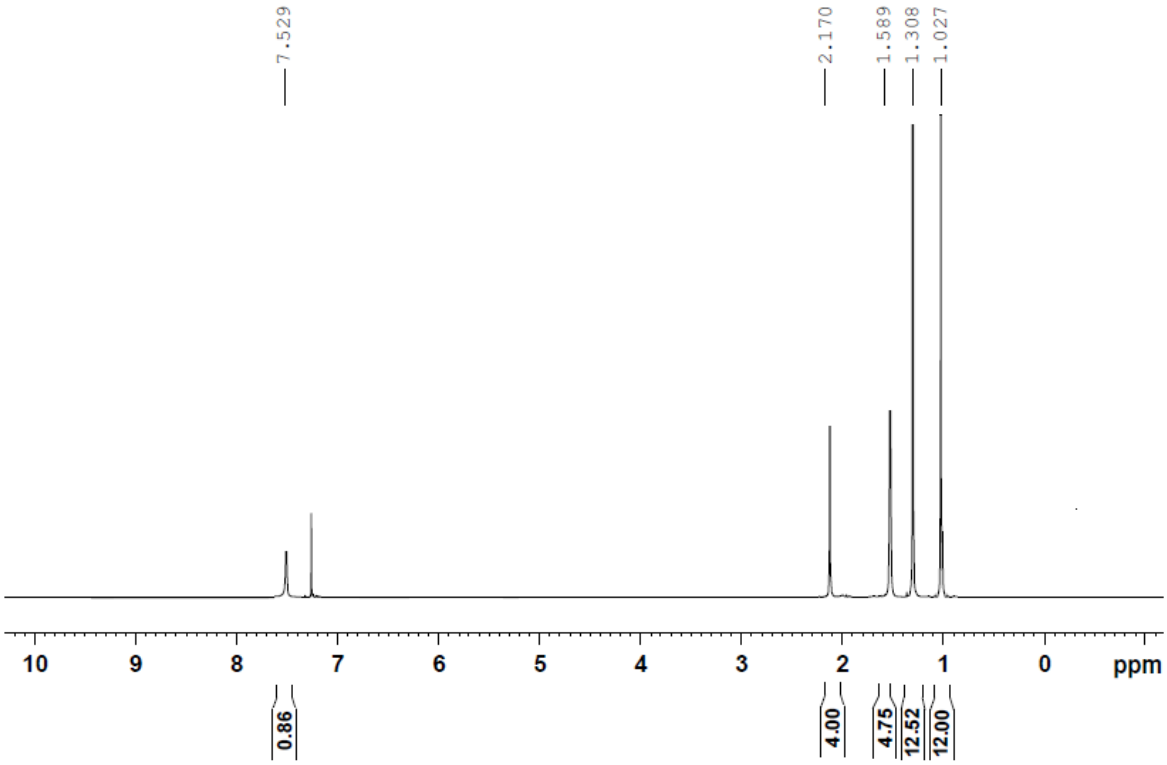


Figure 3. ^{1}H NMR of ligand 9 in $CDCl_3$.

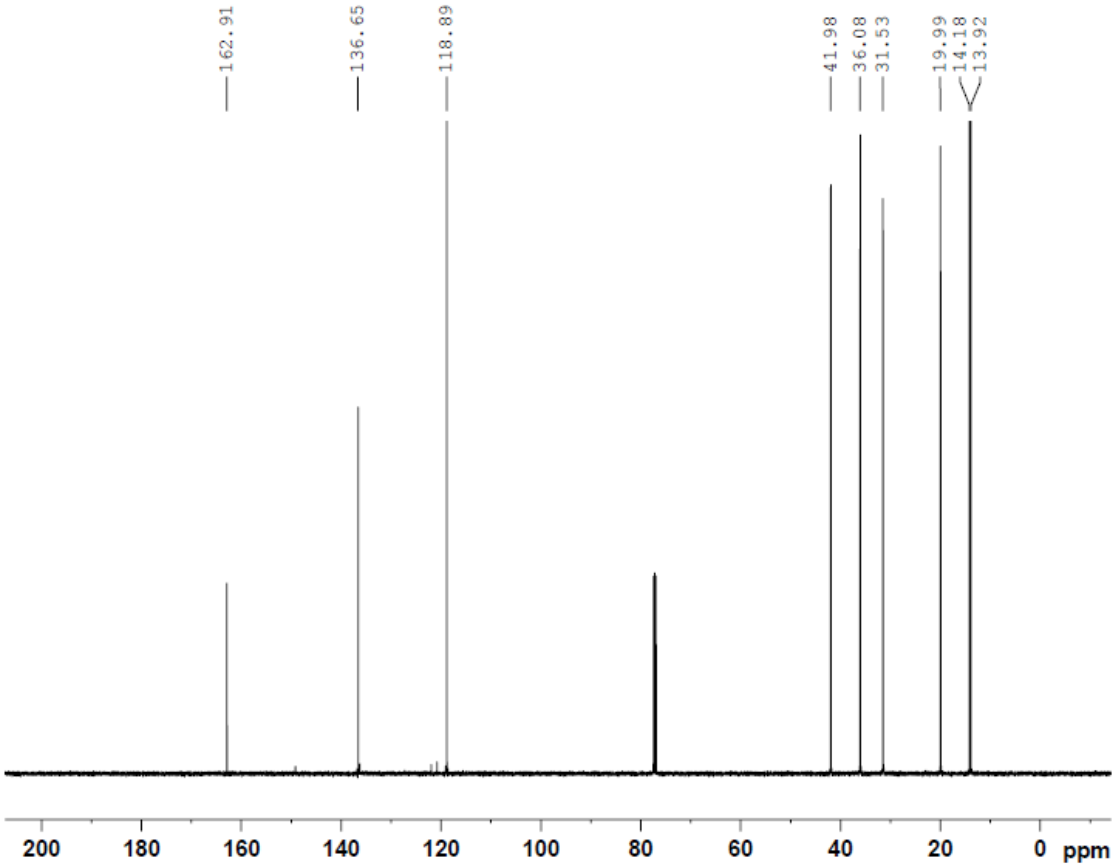
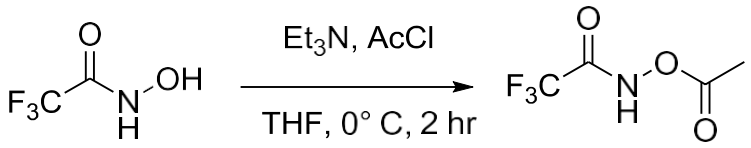


Figure 4. ^{13}C NMR of ligand 9 in $CDCl_3$.

Preparation of $CF_3CONHOAc$



To a stirred solution of 9.7 g (75 mmol, 1.0 equiv) of Trifluoroacetohydroxamic acid ($CF_3CONHOH$) (prepared according to [16]) in 135 mL of THF, 12.4 mL (90 mmol, 1.2 equiv) of triethylamine was added at 0 °C, followed by a dropwise addition of 6.4 mL (90 mmol, 1.2 equiv) of acetyl chloride at 0 °C. The mixture was allowed to stir at room temperature for 2 hours; formation of a white precipitate was observed during the reaction. After the reaction time, the precipitate was removed by filtration. The filtrate was collected and the solvent was removed under vacuum. The residue was then dissolved in 50 mL EtOAc, washed with 1 M HCl (2 x 30 mL), brine (2 x 30 mL) and dried over $MgSO_4$. Removal of solvent under vacuum afforded the off-white, crude product, which was purified by recrystallization from hot toluene. Crystallization overnight at room temperature afforded 9.6 g (75%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 10.47 (br, 1H; NH), 2.22 ppm (s, 3H; CH_3);

^{13}C (NMR 100 MHz, $CDCl_3$, 25 ºC): δ = 167.5, 154.3 (quartet, J =39 Hz), 115.4 (quartet, J =288 Hz), 17.7 ppm;

[16] Middleton, W. J. *J. Org. Chem.*, 1, 3, 4-Dioxazol-2-ones: a potentially hazardous class of compounds, **1983**, *48* (21), 3845–3847

^{19}F (NMR 188.2 MHz,; $CDCl_3$) δ = -73.8 ppm;

IR (ATR): $\tilde{\nu}$ =3157 (s), 3001 (s), 2858 (s), 1811 (s), 1717 (s), 1541 (s), 1371 (s), 1344 (s), 1221 (s), 1192 (s), 1151 (s), 1036 (s), 912 (s), 823 (s), 773 (s), 740 (s), 667 (s), 626 (s) cm^{-1};

HRMS calc. 170.007051.; found 170.007605 (M-H).

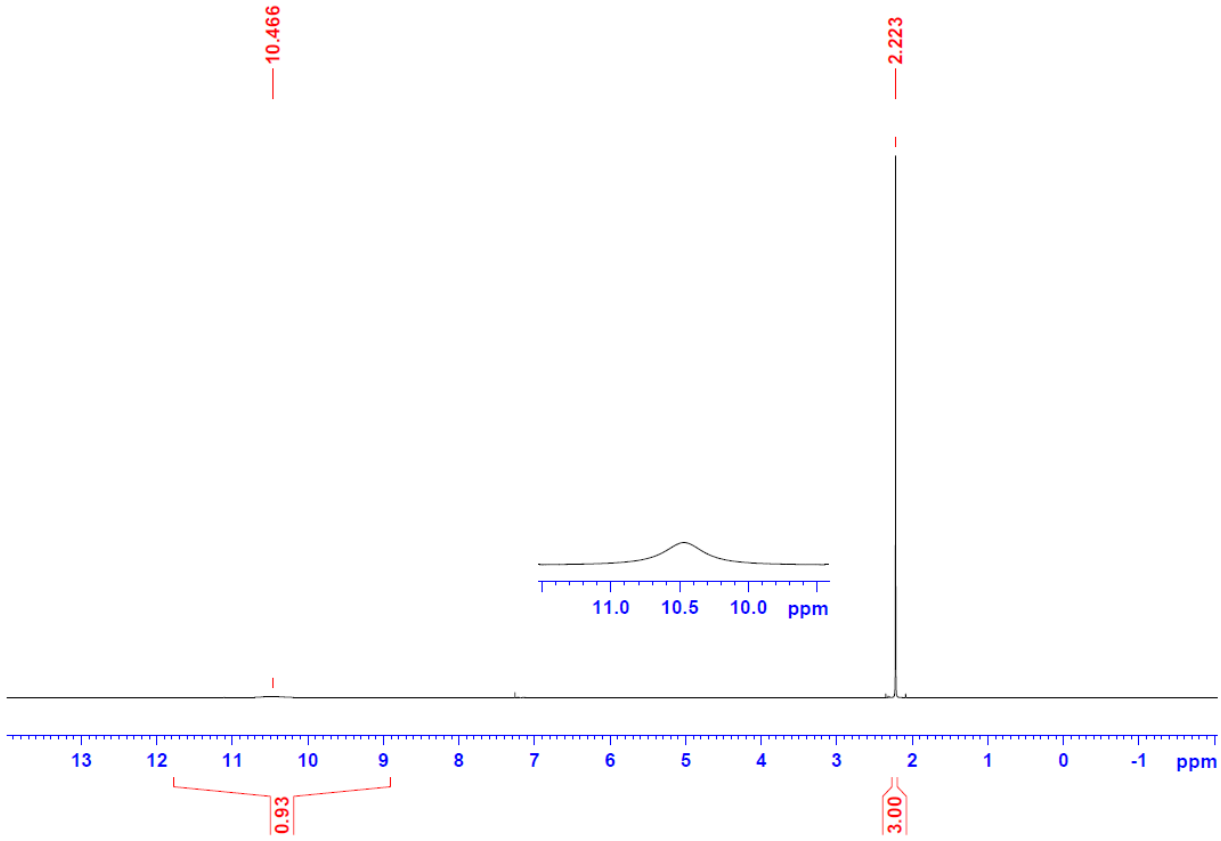


Figure 5. ^{1}H NMR spectrum of $CF_3CONHOAc$ in $CDCl_3$.

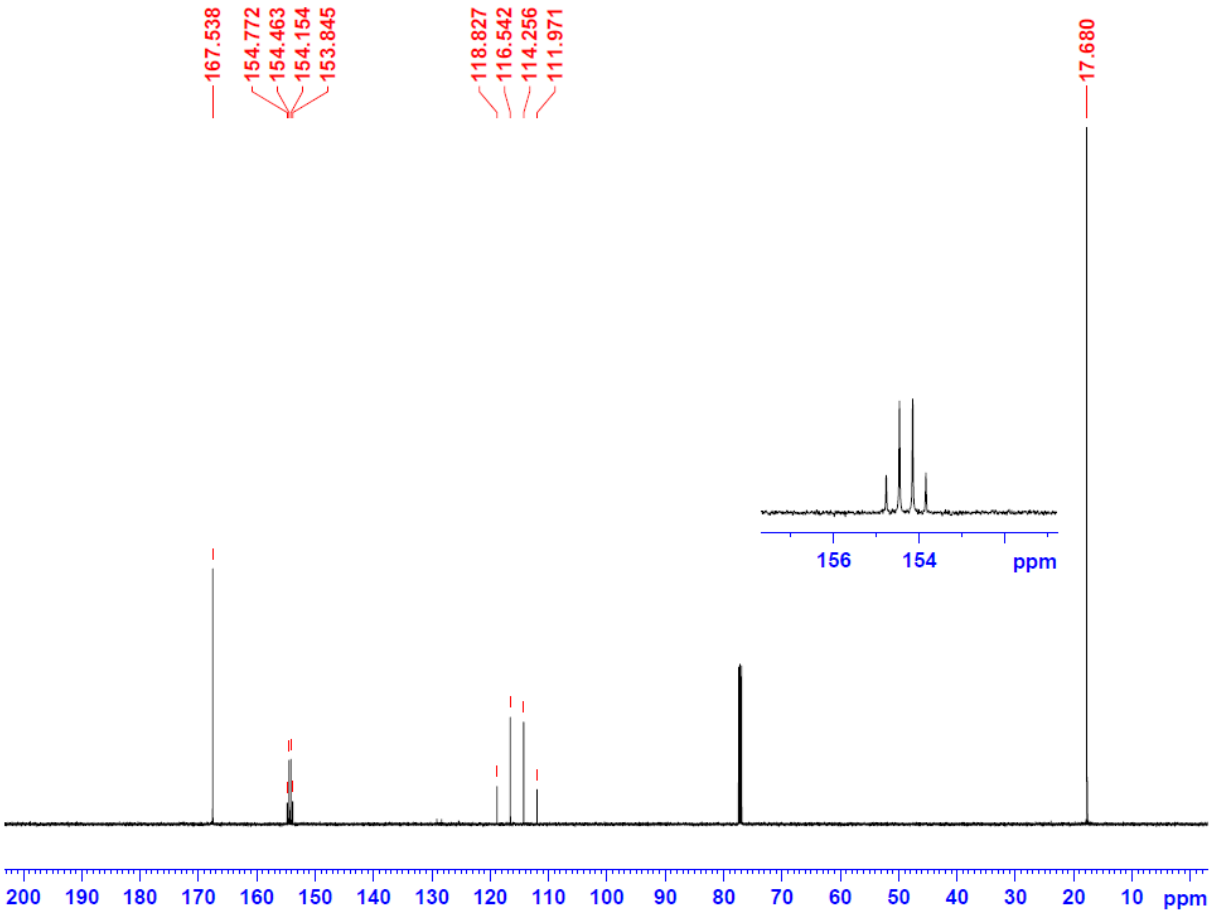


Figure 6. ^{13}C NMR spectrum of $CF_3CONHOAc$ in $CDCl_3$.

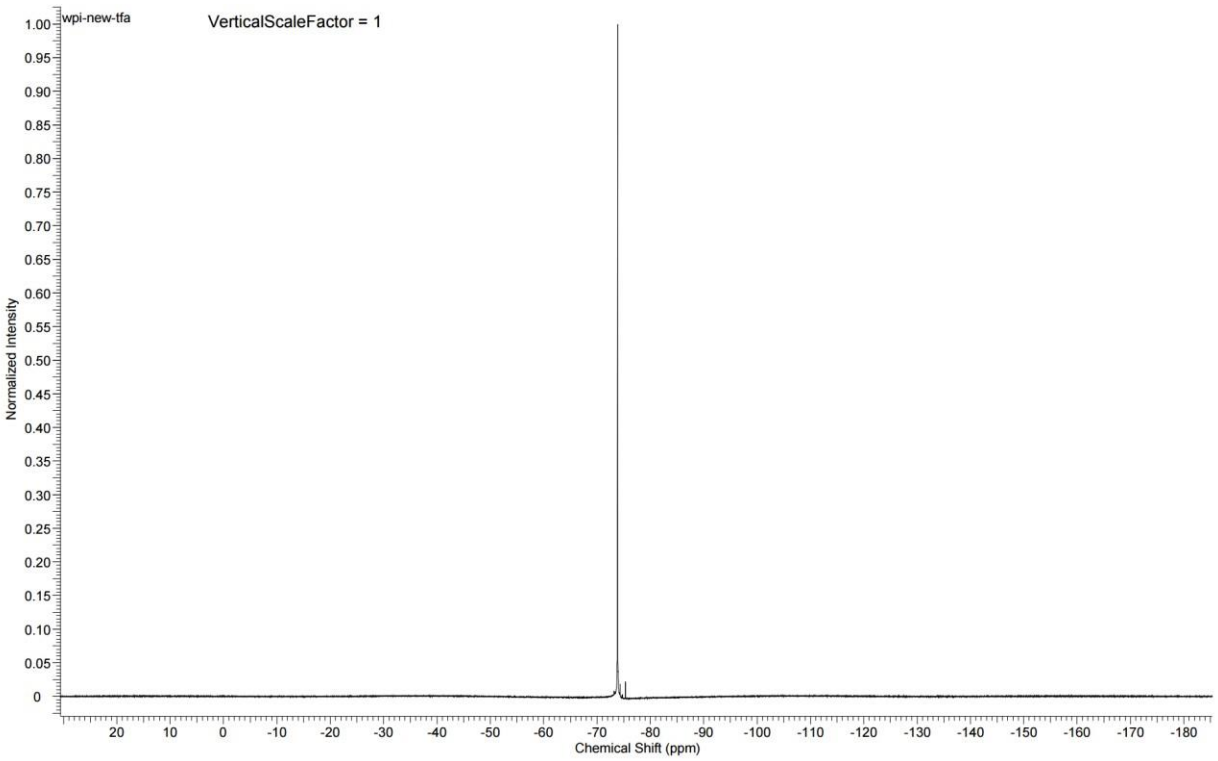
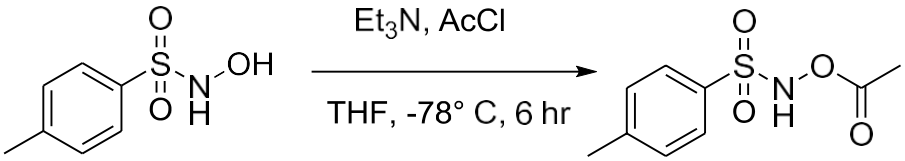


Figure 7. ^{19}F NMR spectrum of $CF_3CONHOAc$ in $CDCl_3$.

Preparation of [(4-methylphenyl)sulfonylamino] acetate (TsNH-OAc)



p-Toluenesulfonylhydroxylamine (TsNHOH) was synthesized in analogy to a reported procedure.[17]

8.0 g (42 mmol, 1.0 equiv) of TsNHOH was dissolved in 280 mL THF at -78° C. Then, 4.4 g (42 mmol, 1.0 equiv) triethylamine was added; acetyl chloride (3.1 mL, 3.3 g, 42 mmol, 1.0 equiv) was then added dropwise to the mixture at the same temperature. Formation of a white precipitate was observed during the addition. The reaction mixture was stirred at -78° C for 6 h; then, the precipitation was removed by filtration. Solvent was removed in vacuum and 150 mL dichloromethane was added. The organic phase was washed with 100 mL 1M HCl, 100 mL H_2O, 100 mL brine and dried over $MgSO_4$. Removal of solvent in vacuum resulted in a slightly yellow, crude product. Recrystallization from EtOAc/hexanes (1:2; 15 mL) in the heat and crystallization at room temperature overnight afforded the title compound (6.0 g; 76%) as a white solid.

[17] Toscano, John P., Art Sutton, Vincent J. Kalish, Frederick Arthur Brookfield, Stephen Martin Courtney, and Lisa Marie Frost. "N-Acyloxysulfonamide and N-Hydroxy-N-Acylsulfonamide Derivatives." U.S. Patent Application 12/962,572, filed December 7, 2010.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.91 (br, 1H; NH), 7.81 ppm (d, 2H; Ar-H), 7.35 ppm (d, 2H; Ar-H), 2.22 ppm (s, 3H; CH_3);

^{13}C (NMR 100 MHz, $CDCl_3$, 25 ºC): δ = 169.1, 146.0, 132.4, 130.1, 128.9, 21.8, 18.3 ppm;

IR (ATR): $\tilde{\nu}$ = 3127 (s), 2795 (s), 2761 (s), 1784 (s), 1764 (s), 1594 (s), 1493 (s), 1425 (s), 1348 (s), 1305 (d), 1192 (s), 1161 (s), 1120 (s), 1089 (s), 1016 (m), 864 (d), 819 (s), 800 (s), 729 (s), 663 (s), 631 (s), cm^{-1};

HRMS calc. 230.048155, found 230.049639 (M+H).

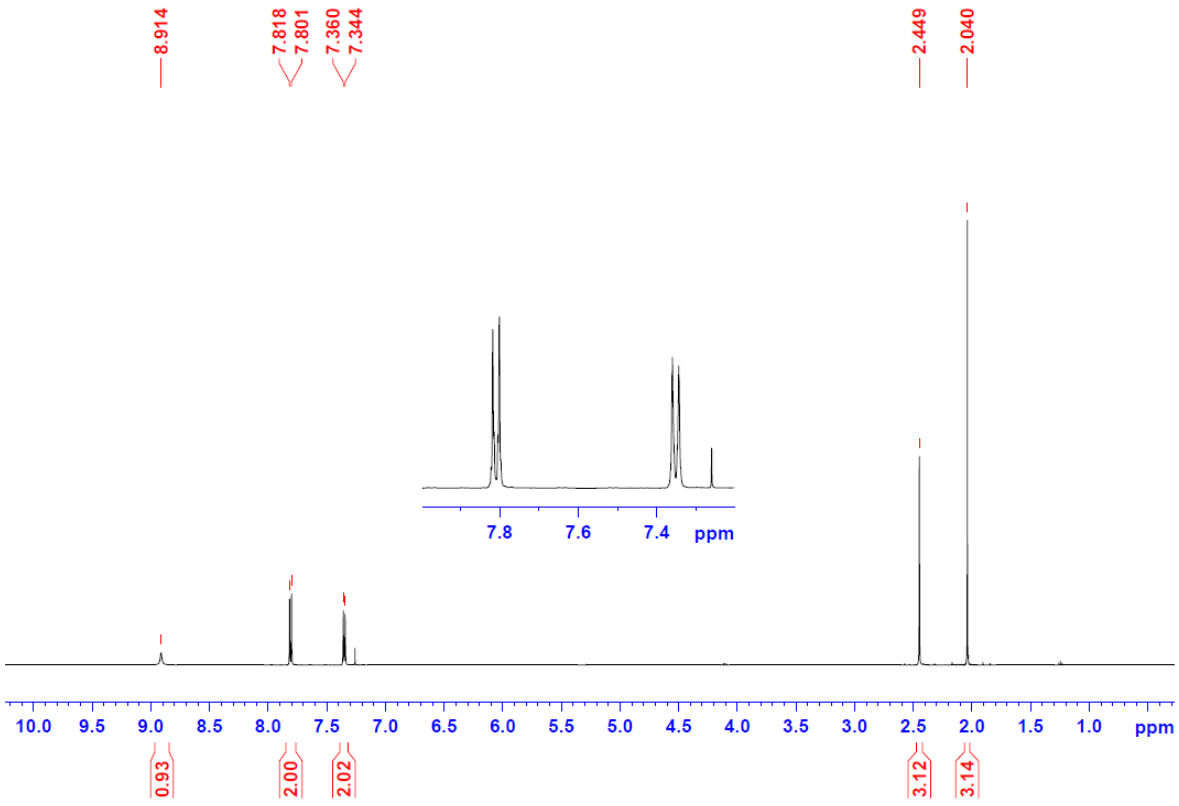


Figure 8. ^{1}H NMR spectrum of [(4-methylphenyl)sulfonylamino] acetate in $CDCl_3$.

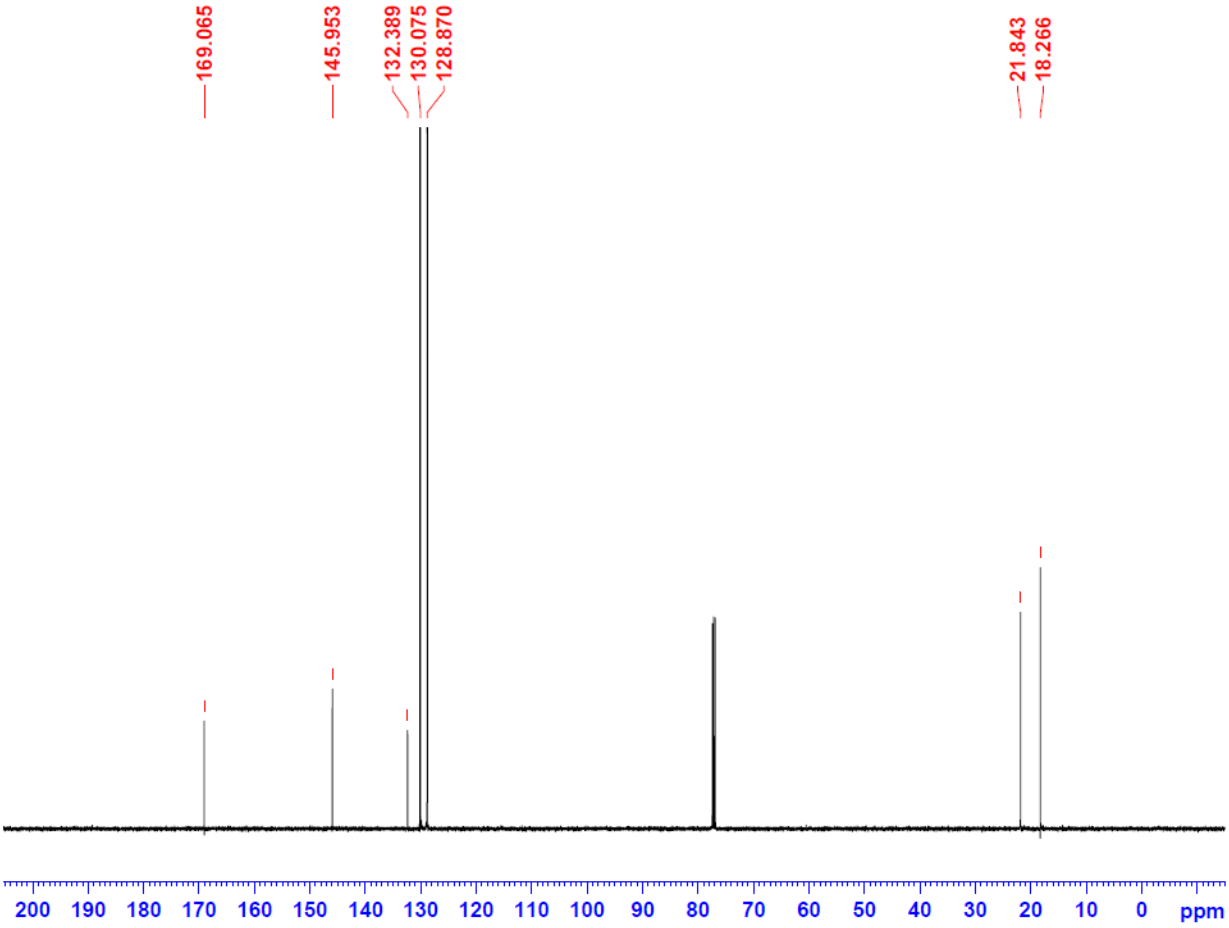
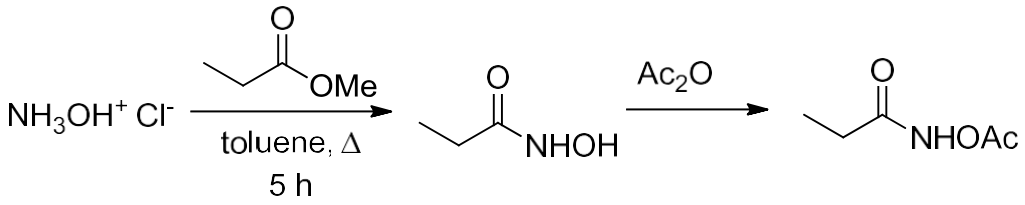


Figure 9. ^{13}C NMR spectrum of [(4-methylphenyl)sulfonylamino] acetate in $CDCl_3$.

Preparation of EtCONH-OAc



EtCONH-OAc was obtained using a modified literature procedure.[18,19]

2.02 g Hydroxylamine hydrochloride (27.6 mmol, 1.0 equiv) and 1.92 g propionamide (27.6 mmol, 1.0 equiv) were mixed in a 250 ml pressure flask, to which 25 ml toluene were added. After tightly sealing the flask, the mixture was heated for 5 h at 100 °C. The reaction mixture was allowed to cool to room temperature and 130 mL hexane were added. The resulting cloudy suspension was sonicated for 5 min. The supernatant liquid was decanted and the remaining solid in the flask was extracted with a 1:1 mixture of EtOAc and acetone (6 × 30 mL) in the heat. All filtrates were combined and the solvent was removed in vacuum. The obtained off-white precipitate was recrystallized from ethyl acetate/hexanes (5:1) in the heat. After letting allow to slowly cool to room temperature,

[18] Allen, C.L.; Atkinson, B.N.; Williams, J.M.J.; Transamidation of Primary Amides with Amines Using Hydroxylamine Hydrochloride as an Inorganic Catalyst, *Angew. Chem. Int. Ed.*, **2012**, *51*(6), 1383-1386

[19] Zhang, Z.; Yu, Y.; Liebeskind, L.S. *N*-Amidation by Copper-Mediated Cross-Coupling of Organostannanes or Boronic Acids with *O*-Acetyl Hydroxamic Acids. *Org Lett*., **2008**, *10*(14), 3005-3008

crystallization was completed at 8° C. The obtained crystals were isolated by filtration to afford 1.82 g of EtCONHOH (78%).

600 mg of N-hydroxy propionamide (EtCONHOH; 6.73 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (18mL). 3.7 mL of a 2 M NaOH solution in H_2O (7.41 mmol, 1.1 equiv) and 0.7 ml Ac_2O (7.41mmol, 1.1 equiv) were added. The mixture was stirred at room temperature for 2 h. The phases were separated and the aqueous phase was repeatedly extracted with CH_2Cl_2, as the title compound shows some solubility in H_2O. The combined organic phases were dried over $MgSO_4$ and the solvent was removed in vacuum. 5ml hexanes were added to the crude product and all solvent was removed again in vacuum. The resulting crystalline product was dissolved in 10 ml EtOAc in the heat. 150 ml hexane were added and the solution was heated to boiling. Slowly allowing to cool to room temperature was followed by completing the crystallization at -20 °C for 18 h. The obtained white crystals of EtCONH-OAc were isolated by filtration and dried in air (3.48 g; 79%).

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 9.153 (br, 1H; NH), 2.26 ppm (m, 2H; C*H*$_2$), 2.22 ppm (s, 3H; C*H*$_3$), 1.2 ppm (t, 3H; C*H*$_3$);

^{13}C (NMR 100 MHz, $CDCl_3$, 25 ºC): δ = 172.37, 168.7, 25.95, 18.18, 9.24 ppm;

IR (ATR): $\tilde{\nu}$ = 3148 (s), 2944 (d), 2889 (s), 1789 (s), 1687 (s), 1529 (s), 1459 (d), 1371 (s), 1238 (s), 1165 (s), 1089 (s), 1078 (s), 1035 (d), 935 (s), 844 (s), 805 (s), 709 (w), 662 (s), cm^{-1};

HRMS calc. 154.0475, found 154.0461 ($C_5H_9NO_3$+Na).

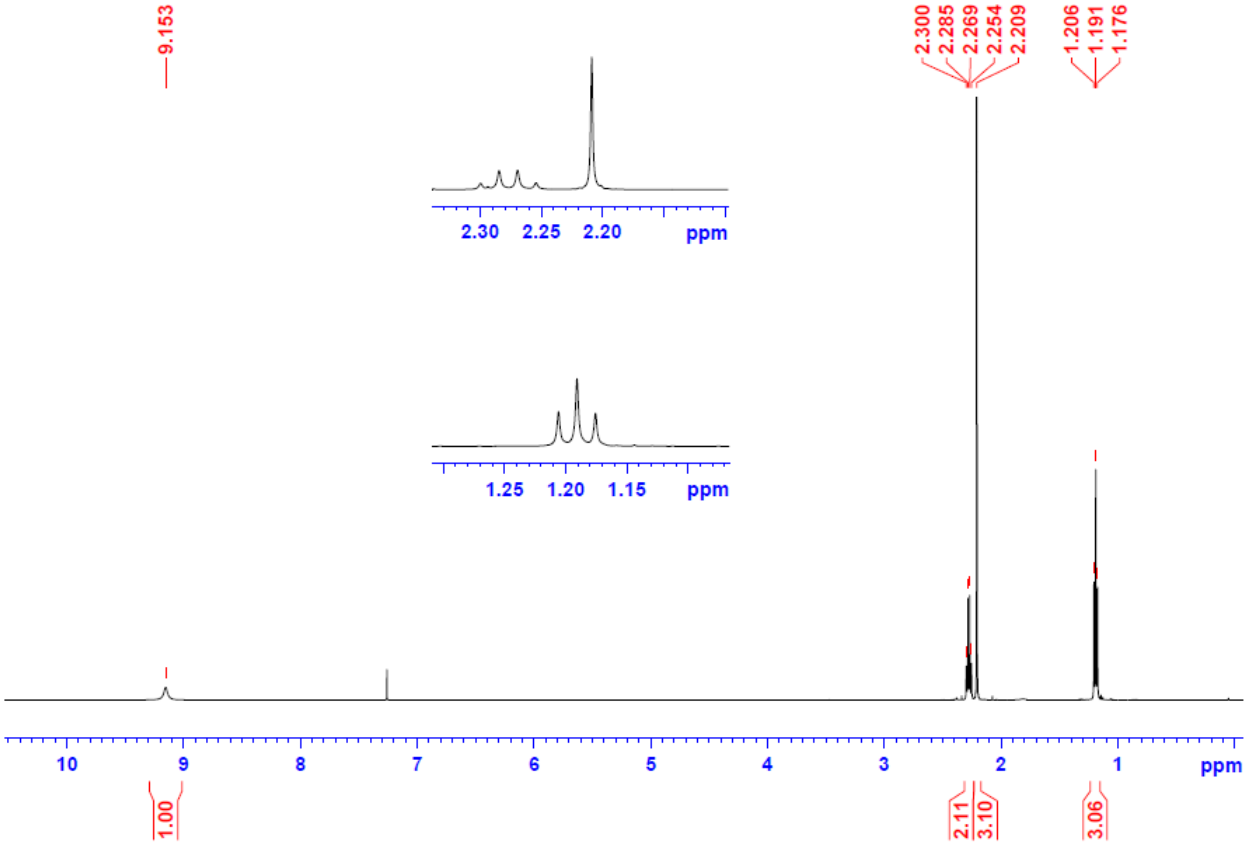


Figure 10. ^{1}H NMR spectrum of EtCONH-OAc in $CDCl_3$.

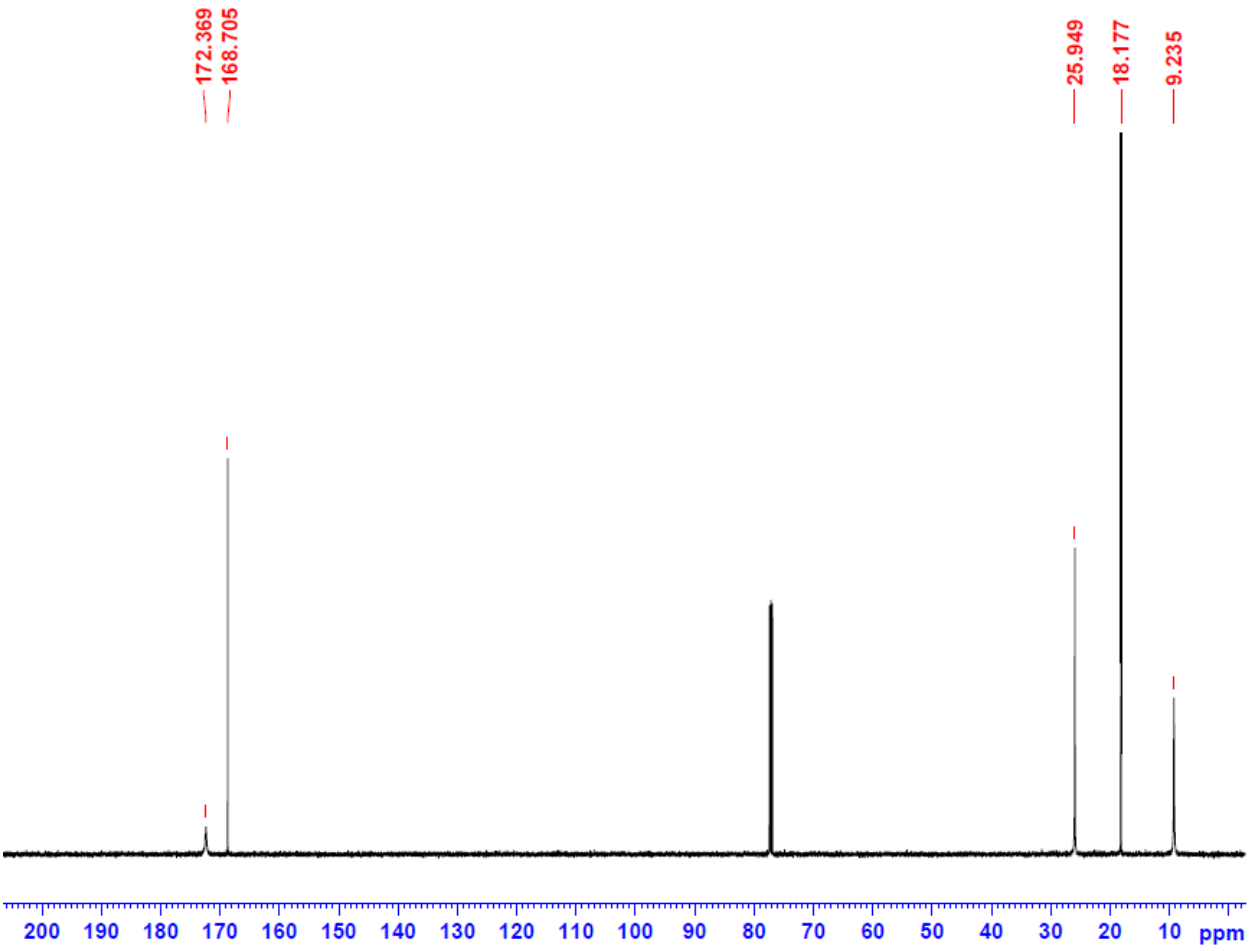
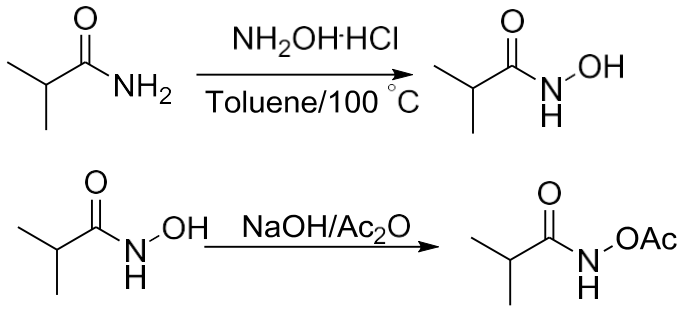


Figure 11. ^{13}C NMR spectrum of Et**CONH-OAc in $CDCl_3$.**

Preparation of ^{i}PrCONH-OAc



^{i}PrNH-OAc was synthesized using a modified literature procedure.[20,21]

Hydroxylamine hydrochloride (2.407 g; 27.6 mmol; 1.00 equiv.) and isobutyramide (1.92 g; 27.6 mmol; 1.00 equiv.) were mixed in a 250 ml pressure flask and 25 ml toluene were added. The flask was sealed and the mixture was heated for 5 hours to 100 °C. The reaction mixture was allowed to cool to room temperature and 130 mL hexanes were added. The obtained cloudy suspension was sonicated for 5 min. The obtained suspension was filtered through a glass filter frit and the filter cake was repeatedly suspended in a 1:1 mixture of EtOAc and acetone (6 × 30 mL) in the heat. All filtrates were combined and the solvent was removed in vacuum. The off-white precipitate obtained was recrystallized from ethyl acetate/hexanes (5:1) in the heat.

[20] Allen, C.L.; Atkinson, B.N.; Williams, J.M.J.; Transamidation of Primary Amides with Amines Using Hydroxylamine Hydrochloride as an Inorganic Catalyst, *Angew. Chem. Int. Ed.*, **2012**, *51*(6), 1383-1386

[21] Zhang, Z.; Yu, Y.; Liebeskind, L.S. *N*-Amidation by Copper-Mediated Cross-Coupling of Organostannanes or Boronic Acids with *O*-Acetyl Hydroxamic Acids. *Org Lett*., **2008**, *10*(14), 3005-3008

After crystallization at room temperature, the obtained crystals were isolated by filtration to afford 2.4 g (78%) of ^{I}PrCONHOH.

496 mg N-hydroxy isobutyramide (4.81 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (15 mL). 2.65 mL of 2 M NaOH in H_2O (5.29 mmol, 212 mg, 1.1 equiv.) and 0.5 mL of Ac_2O (5.29 mmol, 540 mg, 1.1 equiv.) were added. After stirring the mixture at room temperature for 2 h, the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent of the filtrate was removed in vacuum. 5ml hexanes were added to the crude product and the solvent was evaporated in vacuum. The resulting crystalline product was dissolved in 10 ml EtOAc in the heat. 150 ml hexanes were added and the solution was heated to boiling. Crystallization was completed at -20 °C and the resulting white crystals were isolated by filtration, affording 0.55 g (79%) of ^{i}PrCONH-OAc.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.99 (br, 1H; NH), 2.48 ppm (m, 1H; C*H*), 2.22 ppm (s, 3H; CH_3), 1.21 ppm (d, 6H; CH_3);

^{13}C (NMR 100 MHz, $CDCl_3$, 25 ºC): δ = 169.2, 32.8, 19.3, 18.5 ppm;

IR (ATR): $\tilde{\nu}$ = 3134 (s), 2798 (d), 2883 (s), 1795 (s), 1662 (s), 1527 (s), 1472 (d), 1369 (s), 1235 (s), 1168 (s), 1098 (s), 1027 (s), 955 (s), 875 (s), 843 (s), 687 (w), 634 (s), cm^{-1};

HRMS calc. 146.0817, found 146.0812 (M+H).

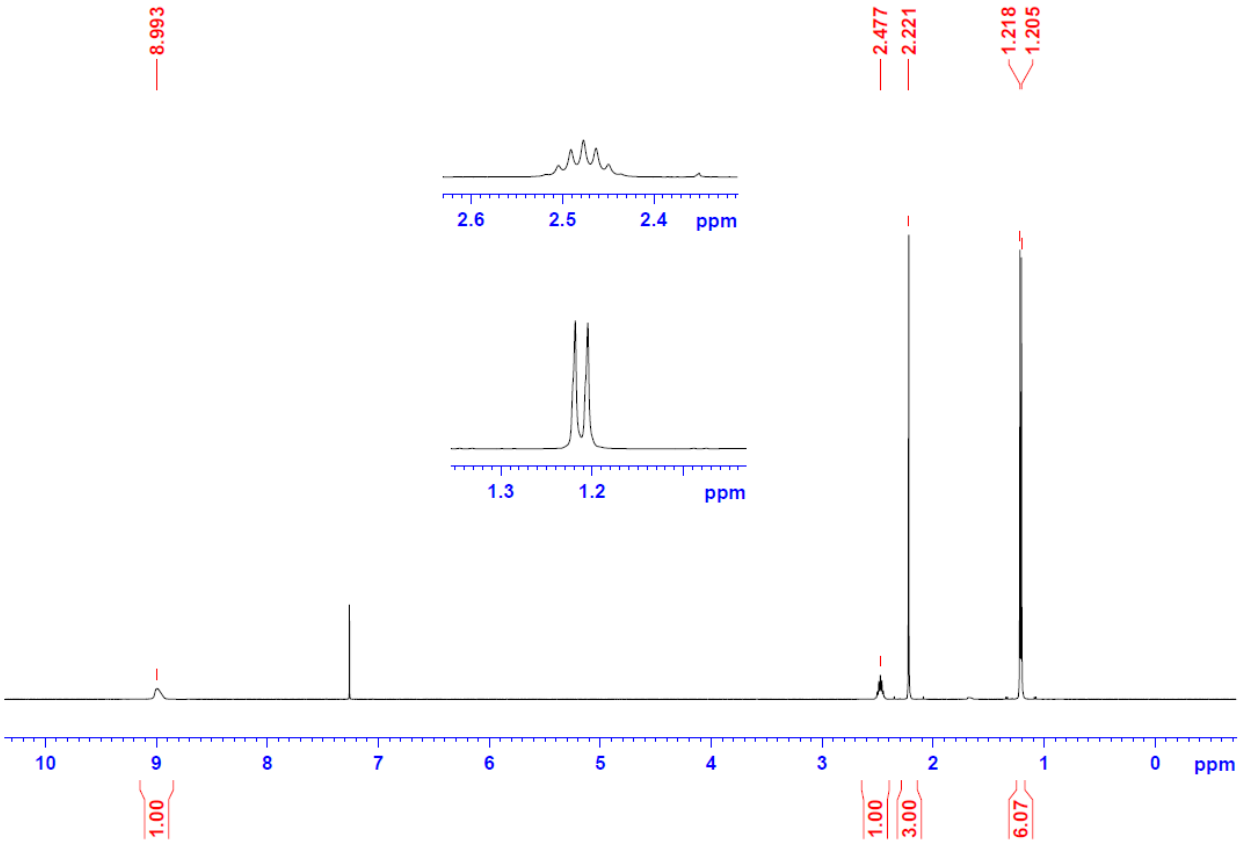


Figure 12. ^{1}H NMR spectrum of ^{i}PrCONH-OAc in $CDCl_3$.

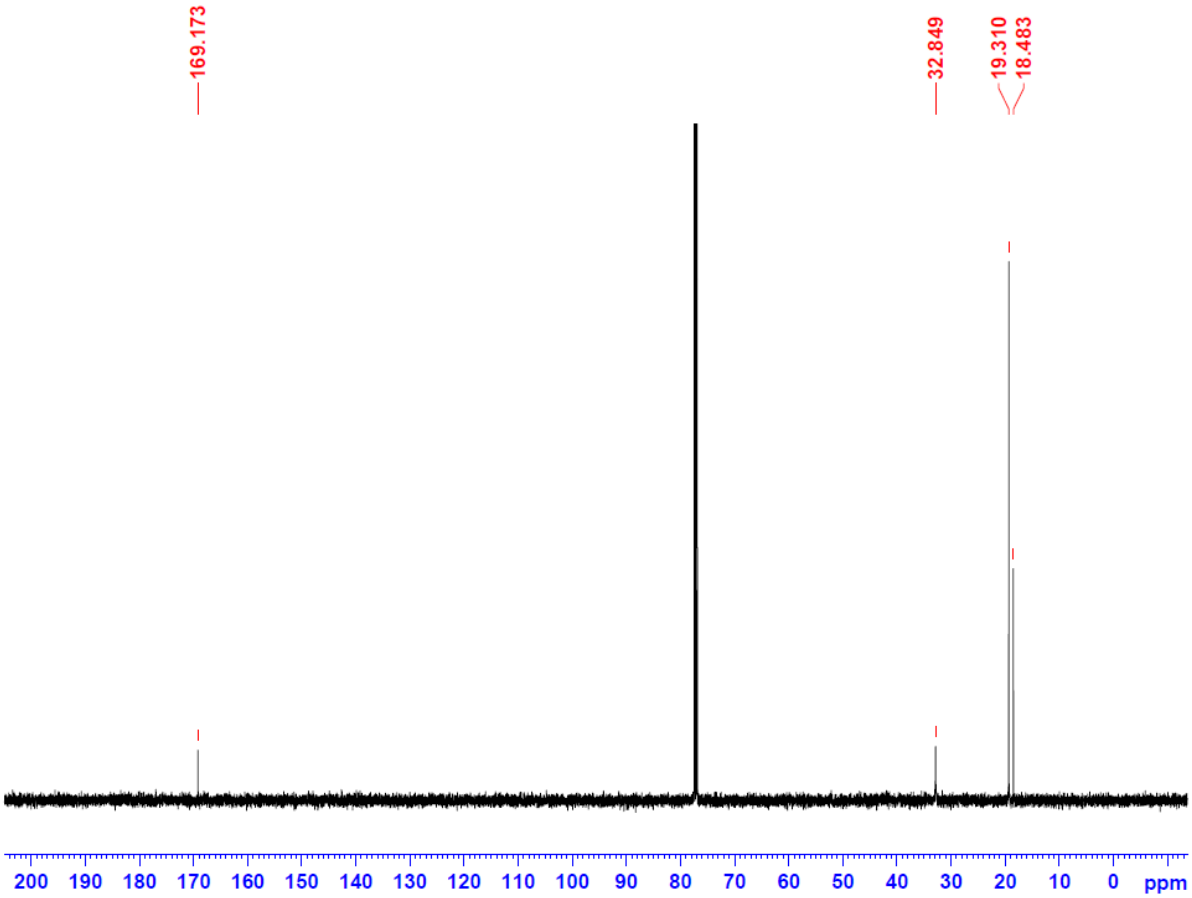


Figure 13. ^{13}C NMR spectrum of ^{i}PrCONH-OAc in $CDCl_3$.

H/D Exchange Reactions Between C_6H_6 and $[D_4]$AcOH

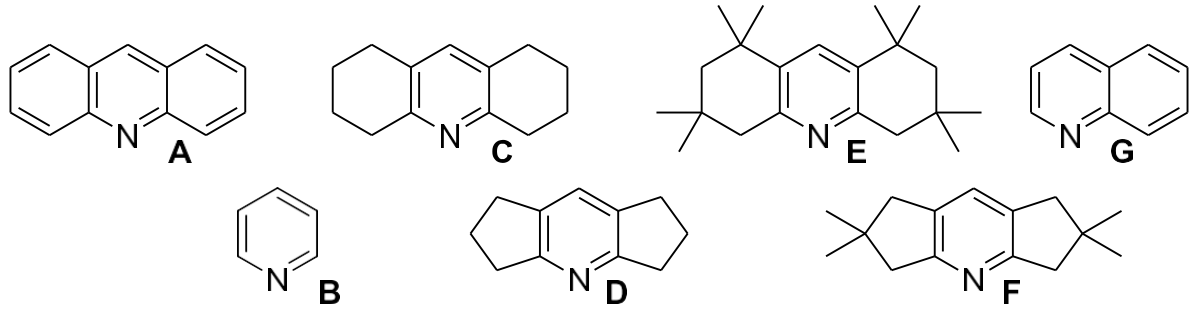


Figure 14. Ligands used in H/D exchange reactions.

H/D exchange reactions were performed according to a literature procedure.[22]

To a 4 mL resealable schlenk tube was added $Pd(OAc)_2$ (1.1 mg, 5.0 μmol, 2.0 mol %), ligand (5.0 μmol, 2.0 mol %) and 0.10 mL (10 μmol, 4.0 mol %) of a stock solution of $AgBF_4$ (19.5 mg, 100 μmol) in 1.0 mL $[D_4]$AcOH, which had been prepared immediately prior to use. An additional 0.27 mL of $[D_4]$AcOH was added, and the mixture was stirred for 1 min. Benzene (22.3 μL, 19.5 mg, 0.250 mmol, 1.00 equiv), stored over 4 Å molecular sieves, was added to the reaction vessel, which was subsequently sealed. The vessel was completely submerged in a preheated oil bath. At the end of the reaction, the vessel was cooled to room temperature. The reaction mixture was then filtered over a plug of Celite to remove any particulates and rinsed with EtOAc (1 x 2 mL) into a 20 mL scintillation vial. A saturated aqueous solution of

[22] H/D exchange was conducted using a standard procedure developed previously: A. J. Hickman, J. M. Villalobos, M. S. Sanford, *Organometallics* **2009**, *28*, 5316-5322.

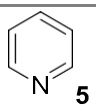
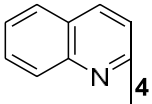
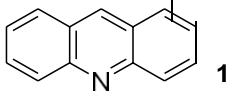
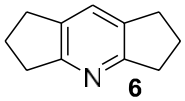
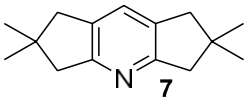
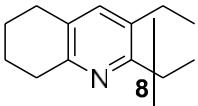
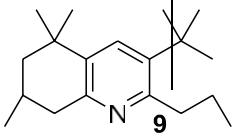
K_2CO_3 (9 M in deionized H_2O, 2 x 1 mL) was added to the vial to quench and separate the acid. The organic layer was carefully separated and diluted with additional EtOAc to give a 12.8 mM solution of benzene (~1 mg/mL) for analysis by GC-MS.

The % deuterium incorporation was defined as the percent of C–H bonds converted to C–D bonds. Background reactions (in the absence of any metal catalyst) at 150 °C and 100 °C are minimal with $[D_4]$AcOH (<0.5 TON) and are documented in the literature.[22,23]

Turnover numbers (TONs) are calculated as mol deuterium incorporated per mol of catalyst. The reported error is the standard deviation of at least two replicate trials.

[23] M. H. Emmert, J. B. Gary, J. M. Villalobos, M. S. Sanford, *Angew. Chem. Int. Ed.* **2010**, *49*, 5884-5886.

Table 3. Turnover numbers for H/D exchange between benzene and [D_4]AcOH at 100 °C catalyzed by $Pd(OAc)_2$/ligand combinations (1:1) after 2 and 24 h.
Conditions: $Pd(OAc)_2$ (1.1 mg, 5.0 μmol, 2.0 mol %), ligand (5.0 μmol, 2.0 mol %), benzene (22.3 μl, 0.25 mmol, 1.00 equiv), [D_4]AcOH (0.37 ml, 6.5 mmol, 25 equiv), 100 °C.

Ligand	TON 2 h	TON 24 h
 5	5 ± 1	33 ± 3
 4	9 ± 1	32 ± 1
 1	11 ± 1	21 ± 1
 6	3.7 ± 0.4	3.5 ± 0.1
 7	4 ± 2	10 ± 1
 8	7 ± 2	12.1 ± 0.1
 9	4.3 ± 0.3	6 ± 3

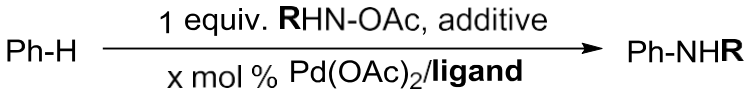
Optimization of C-H Amination

To a scintillation vial (5 mL) was added benzene (0.50 mL, 5.6 mmol, 40 equiv; or 0.75 mL, 8.4 mmol, 60 equiv.), palladium acetate (10 to 15 mol %), ligand (10 to 18 mol %) and amination reagent (140 μmol, 1.0 equiv). The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. The reaction was allowed to cool to room temperature.

Product Analysis by NMR (for synthesis of PhNHAc): 0.50 mL (corresponding to 5.0 mg; 29 μmol of 1,3-dinitrobenzene) of a standard solution containing NMR solvent and 1,3-dinitrobenzene as NMR standard (50 mg; 290 μmol in 5.0 mL of $CDCl_3$) were added to the mixture. The resulting solution was filtered through celite. The amount of product formed was determined by integration of the NMR signals at 8.97 ppm (1H, 1,3-dinitrobenzene) and 2.21 ppm (3H, PhNHC(O)$\underline{CH_3}$) (relaxation time = 15.0 s, NS = 16).

Product Analysis by GC (for synthesis of PhNHC(O)CF_3): 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL saturated, aqueous K_2CO_3 solution. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. The amount of product formed was determined by calibrated GC analysis.

Table 4. Calibrated GC Yields of C-H Amination with Bulky Ligands. Conditions: benzene (40 or 60 equiv), $Pd(OAc)_2$ (10 to 15 mol %), ligand (10 to 18 mol %) and amination reagent (140 μmol, 1.0 equiv), 100 °C, 24 hr.



Additive	Amination Reagent	Equivalent Benzene	mol % $Pd(OAc)_2$	Ligand (mol %)	Yield PhNHR
none	AcO-NHAc	40	10	**1** (10)	11 ± 1%
0.6 eq AcOH	"	"	"	"	27 ± 2%
1.0 eq AcOH	"	"	"	"	29 ± 2%
1.3 eq AcOH	"	"	"	"	25 ± 2%
5 mol % AgOAc	"	"	"	"	27 ± 1%
10 mol % AgOAc	"	"	"	"	20 ± 2%
none	AcO-NHC(O)CF_3	"	"	**1** (10)	21± 2%
1 eq AcOH	"	"	"	"	22 ± 2%
5 mol % AgOAc	"	"	"	"	23 ± 1%
1.0 eq AcOH	AcO-NHAc	"	"	**4** (10)	16 ± 1%
5 mol % AgOAc	"	"	"	"	29 ± 1%
10 mol % AgOAc	"	"	"	"	29 ± 1%
1.0 eq AcOH	AcO-NHAc	"	"	**5** (10)	16 ± 1%
5 mol % AgOAc	"	"	"	"	29 ± 1%
10 mol % AgOAc	"	"	"	"	30 ± 1%
none	AcO-NHAc	40	10	**8** (10)	12 ± 3%
1 eq AcOH	"	"	"	"	45 ± 3%
5 mol % AgOAc	"	"	"	"	40 ± 2%
none	AcO-NHC(O)CF_3	"	"	**8** (10)	13 ± 2%
1 eq AcOH	"	"	"	"	43 ± 2%
5 mol % AgOAc	"	"	"	"	46 ± 2%
none	AcO-NHAc	40	10	**6** (10)	13 ± 2%
0.2 eq AcOH	"	"	"	"	40 ± 3%
5 mol % AgOAc	"	"	"	"	42 ± 2%

none	AcO-NHC(O)CF_3	"	"	**6** (10)	19 ± 3%
0.2 eq AcOH	"	"	"	"	32 ± 2%
0.4 eq AcOH	"	"	"	"	34 ± 3%
0.6 eq AcOH	"	"	"	"	31 ± 2%
1.0 eq AcOH	"	"	"	"	27 ± 2%
2.5 mol % AgOAc	"	"	"	"	22 ± 3%
5 mol % AgOAc	"	"	"	"	44 ± 2%
10 mol % AgOAc	"	"	"	"	31 ± 3%
none	AcO-NHAc	40	10	**9** (10)	11± 1%
1 eq AcOH	"	"	"	"	31 ± 2%
1 eq AcOH, 90 °C	"	"	"	"	23 ± 2%
1 eq AcOH, 80 °C	"	"	"	"	7 ± 2%
0.4 eq AcOH	"	"	"	"	34 ± 2%
0.2 eq AcOH	"	"	"	"	36 ± 2%
0.1 eq AcOH	"	"	"	"	29 ± 1%
5 mol % AgOAc	"	"	"	"	43 ± 2%
5 mol % AgOAc	"	"	"	**9** (15)	33± 2%
5 mol % AgOAc	"	60	"	**9** (15)	37 ± 2%
5 mol % AgOAc	"	"	15	**9** (18)	42 ± 3%
none	AcO-NHC(O)CF_3	40	10	**9** (10)	14 ± 2%
1 eq AcOH	"	"	"	"	39 ± 3%
5 mol % AgOAc	"	"	"	"	31 ± 1%
5 mol % AgOAc	"	"	"	**9** (15)	35 ± 2%
5 mol % AgOAc	"	60	"	**9** (15)	39 ± 3%
5 mol % AgOAc	"	"	15	**9** (18)	43 ± 2%
none	AcO-NHAc	40	10	**7** (10)	15 ± 2%
0.2 eq AcOH	"	"	"	"	31 ± 3%
0.4 eq AcOH	"	"	"	"	42 ± 2%
0.6 eq AcOH	"	"	"	"	40 ± 2%
2.5 mol % AgOAc	"	"	"	"	23 ± 2%
5 mol % AgOAc	"	"	"	"	47 ± 1%
10 mol % AgOAc	"	"	"	"	34 ± 2%
5 mol % AgOAc	"	"	"	**7** (15)	50 ± 2%
5 mol % AgOAc	"	60	"	**7** (15)	51 ± 2%
5 mol % AgOAc	"	"	15	**7** (18)	52 ± 3%
7.5mol % AgOAc	"	"	15	**7** (18)	49 ± 2%
10 mol % AgOAc	"	"	15	**7** (18)	33 ± 2%

none	AcO-NHC(O)CF_3	40	10	**7** (10)	25 ± 1%
0.2 eq AcOH	"	"	"	"	34 ± 3%
0.4 eq AcOH	"	"	"	"	35 ± 2%
0.6 eq AcOH	"	"	"	"	29 ± 2%
2.5 mol % AgOAc	"	"	"	"	28 ± 2%
5 mol % AgOAc	"	"	"	"	48 ± 2%
10 mol % AgOAc	"	"	"	"	36 ± 3%
5 mol % AgOAc	"	"	"	**7**(15)	52 ± 2%
"	"	"	"	**7** (20)	41 ± 3%
"	"	"	15	**7** (18)	44 ± 3%
"	"	50	"	"	50± 1%
"	"	60	"	"	53 ± 2%
"	"	"	"	**7** (15)	50 ± 2%
"	"	"	"	**7** (20)	42± 2%
7.5mol % AgOAc	"	"	"	**7** (18)	51 ± 3%
10 mol % AgOAc	"	"	"	"	35 ± 2%
2.5 mol % NMe_4BF_4	"	"	"	"	40 ± 2%
5 mol % NMe_4BF_4	"	"	"	"	37± 2%
7.5 mol % NMe_4BF_4	"	"	"	"	22± 3%

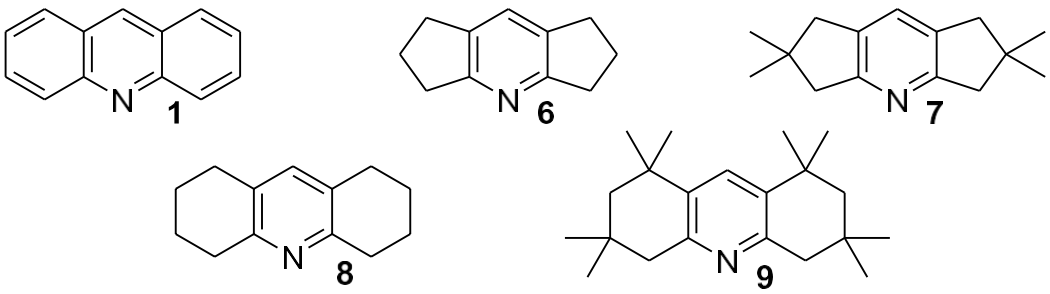
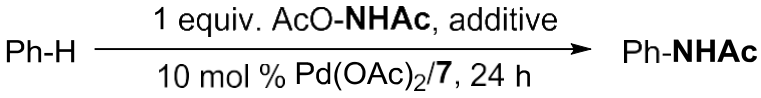


Figure 15. Ligands used in Reaction Optimization.

Study of Additive Effects

In analogy to the conditions established above, benzene (0.50 mL, 5.6 mmol, 40 equiv), Pd(OAc)2 (3.1 mg, 14 μmol, 10 mol %), additive (5.0 - 10 mol %), ligand 7 (10 mol %) and AcO-NHAc (1.0 equiv) were added to a scintillation vial (5 mL). The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. The reaction was allowed to cool to room temperature. Product yields were determined by calibrated ^{1}H NMR analysis and are tabulated in Scheme 1.



additive	Yield[a]
5 mol % AgOAc	47%
10 mol % "	34%
5 mol % $AgSbF_6$	23%
5 mol % NBu_4OAc	17%
10 mol % NMe_4OAc	18%
5 mol % $AgSbF_6/NBu_4OAc$	28%
5 mol % NMe_4BF_4	20%

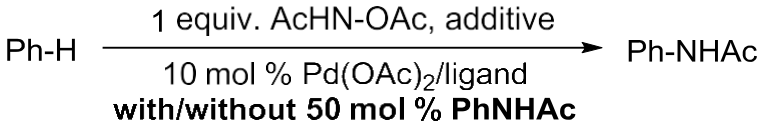
[a]Conditions: 40 equiv. PhH, 100 °C.

Scheme 1. Additive Effects on C-H Amination with $Pd(OAc)_2$/7.

Product Inhibition Study

To a scintillation vial (5 mL) was added C_6H_6 (0.50 mL, 5.6 mmol, 40 equiv.), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 110 mol %), ligand (14 μmol, 10 mol %) and AcO-NHAc (16.0 mg, 140 μmol, 1.0 equiv). To evaluate the effect of product presence on C-H amination activity, PhNHAc (9.5 mg, 70 μmol, 0.50 equiv) was added. The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 24 h. The reaction was allowed to cool to room temperature. 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL saturated, aqueous K_2CO_3 solution. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. The product yield was determined by calibrated GC analysis.

Table 5. GC Yields for Product Inhibition Study. Conditions: C_6H_6 (40 equiv), $Pd(OAc)_2$ (10 mol %), ligand (10 mol %), AcNH-OAc (1.0 equiv), 100 °C, 24 h.



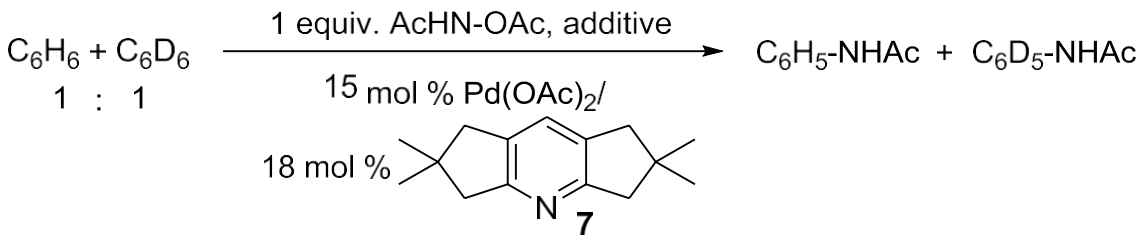
Conditions/Additive	GC Yield of newly formed PhNHAc
Ligand **1**, 1.0 eq. AcOH	29%
Ligand **1**, 1.0 eq. AcOH, 50 mol % PhNHAc	10%
Ligand **8**, 1.0 eq. AcOH	45%
Ligand **8**, 1.0 eq. AcOH, 50 mol % PhNHAc	18%
Ligand **9**, 1.0 eq. AcOH	31%
Ligand **9**, 1.0 eq. AcOH, 50 mol % PhNHAc	17%

Competition Kinetic Isotope Effect Study

To a scintillation vial (5 mL) was added C_6H_6 (0.37 mL, 330 mg, 4.2 mmol, 30 equiv.), C_6D_6 (0.37 mL, 350 mg, 4.2 mmol, 30 equiv.), $Pd(OAc)_2$ (4.7 mg, 21 μmol, 15 mol %), ligand **7** (5.4 mg, 25 μmol, 18 mol %) and AcO-NHAc (16.0 mg, 140 μmol, 1.0 equiv). The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 2, 4, or 24 hr. The reaction was allowed to cool to room temperature. 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL saturated, aqueous K_2CO_3 solution. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. The product yield was determined by calibrated GC analysis.

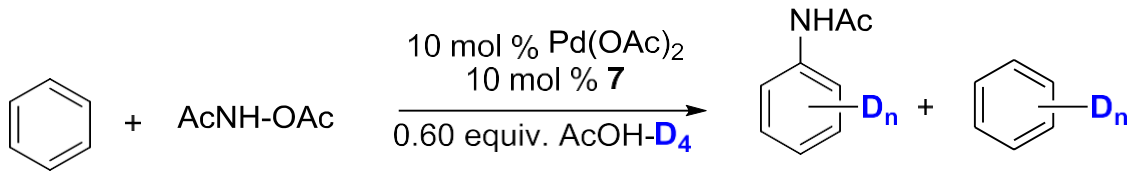
The competition kinetic isotope effect was determined by measuring the ratio of deuterated and non-deuterated products through GCMS analysis, using the ratios of the mass peaks at m/z = 135 (C_6D_5-NHAc) and m/z = 140 (C_6H_5-NHAc) (see Table 6)

Table 6. Kinetic Isotope Effect After Different Reaction Times. Conditions: C_6H_6 (30 equiv), C_6D_6 (30 equiv), $Pd(OAc)_2$ (15 mol %), ligand **7** (18 mol %) and amination reagent (140 μmol, 1.0 equiv), 100 °C, 24 hr.



Reaction Time	GC Yield	KIE = (m/z C_6D_5-NHAc)/ (m/z C_6H_5-NHAc)
2 h	11 ± 2%	3.01
4 h	24 ± 1%	2.88
24 h	53 ± 2%	2.57

C-H Amination of Benzene in Presence of AcOH-D_4



In analogy to the conditions established above (Table 4), benzene (0.50 mL, 438 mg, 5.6 mmol, 40 equiv.), $Pd(OAc)_2$ (3.1 mg, 14 µmol, 10 mol %), AcOH-D_4 (5.1 µL, 5.4 mg, 84 µmol, 0.60 equiv.), ligand **7** (3.0 mg, 14 µmol, 10 mol %) and AcNH-OAc (16.4 mg, 0.14 mmol, 1.0 equiv.) were added to a scintillation vial. The vial was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and heated to 100 °C for 24 h. The reaction was then allowed to cool to room temperature. Et_2O was added and the mixture was filtered through celite and was directly analyzed by GCMS.

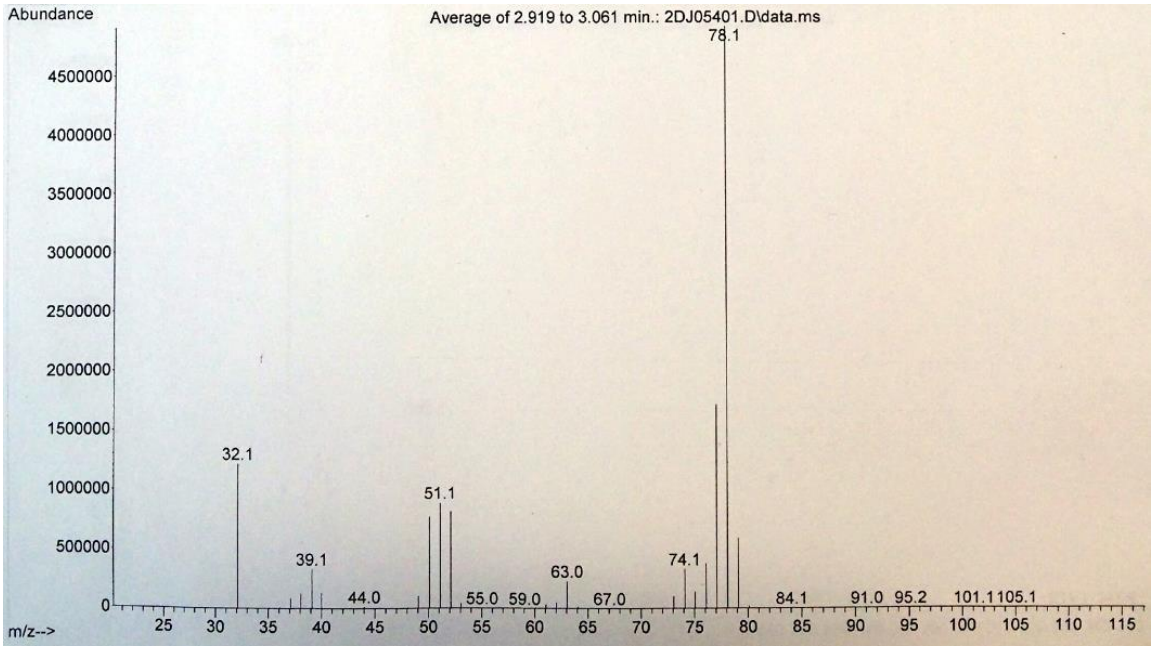


Figure 16. GCMS Spectrum of Benzene Remaining in the Reaction Mixture.

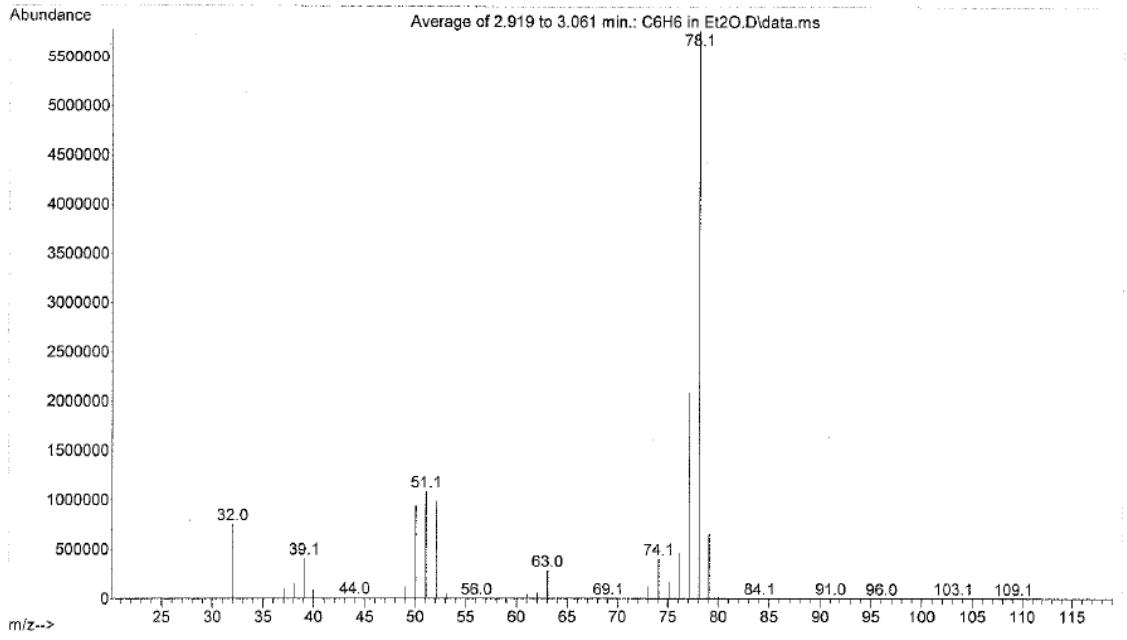


Figure 17. GCMS Spectrum of Commercial Benzene used as Solvent in the Reaction.

Table 7. Abundance of m/z 78 to 84 for C6H6 recovered from reaction in presence of AcOH-D_4 vs. unreacted benzene used as solvent.

m/z	Relative Abundance	
	Commerical C_6H_6	C_6H_6 recovered from reaction in presence of AcOH-D_4
78	89.52%	88.86%
79	10.16%	10.74%
80	0.30%	0.37%
81	0.01%	0.01%
82	0.00%	0.00%
83	0.00%	0.00%
84	0.00%	0.01%

Based on the data above and the fragmentation of unreacted benzene-D_6, the isotope distribution (Table 8) was calculated by deconvolution of GCMS raw data using a benzene H/D exchange worksheet reported by Periana and coworkers.[24] Quantities of each isotopomer and the corresponding equivalent values are calculated based on the remaining amount of benzene in the reactions mixture (0.504 mmol), which is the difference between the initial amount of C_6H_6 (5.6 mmol) and the amount of PhNHAc produced (40%, 0.056 mmol; see Table 4 above).

[24] Young, K. J. H.; Meier, S. K.; Gonzales, J. M.; Oxgaard, J.; Goddard, W. A.; Periana, R. A., *Organometallics* **2006,** *25* (20), 4734-4737.

Table 8. Calculated Isotope Distribution of Benzene Recovered from Reaction Mixture.

Isotope	C_6H_6	C_6H_5D	$C_6H_4D_2$	$C_6H_3D_3$	$C_6H_2D_4$	C_6HD_5	C_6D_6
Abundance	99.22%	0.75%	0.00%	0.01%	0.00%	0.00%	0.01%
equivalent (based 0.14 mmol AcNH-OAc = 1.00 equiv.)	39.29	0.30	0.00	0.00	0.00	0.00	0.00

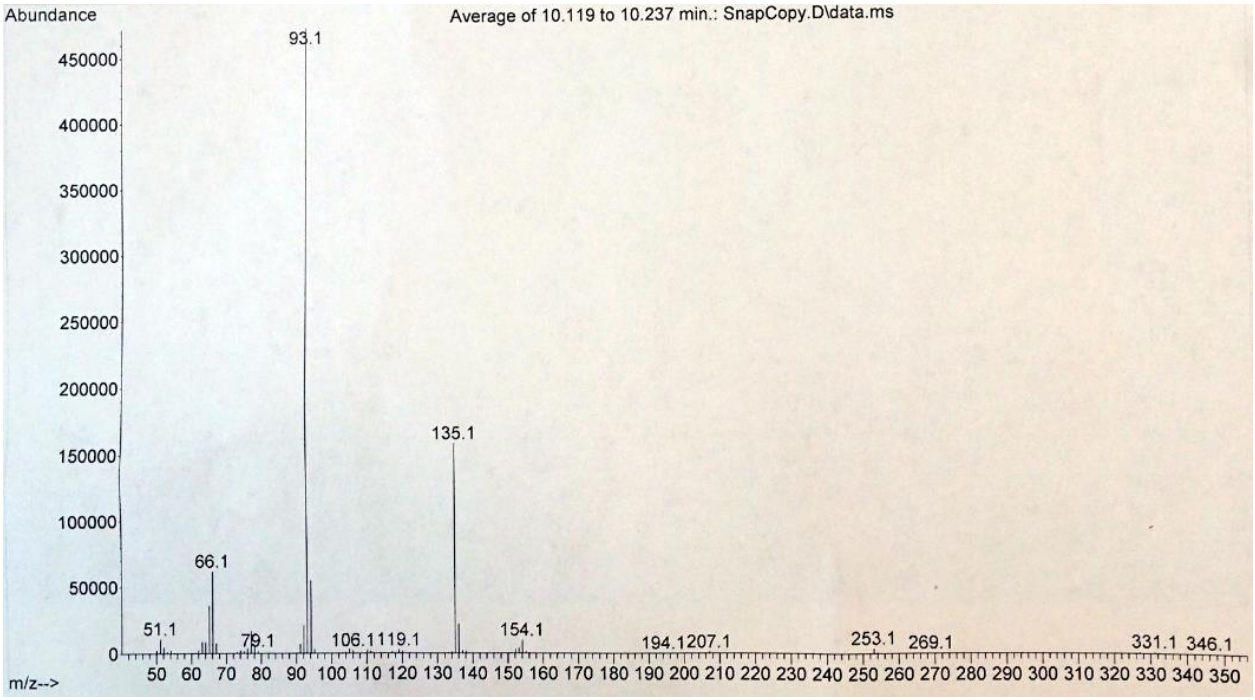


Figure 18. GCMS Spectrum of Ph-NHAc from Reaction in the Presence of AcOH-D_4.

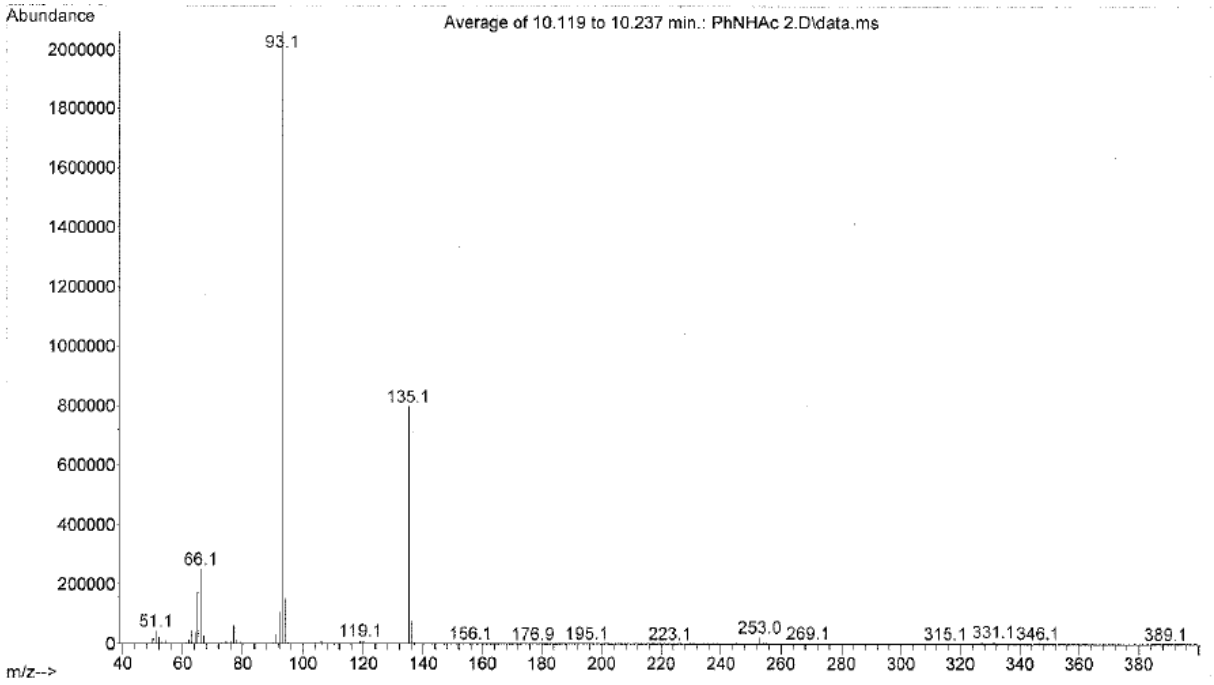
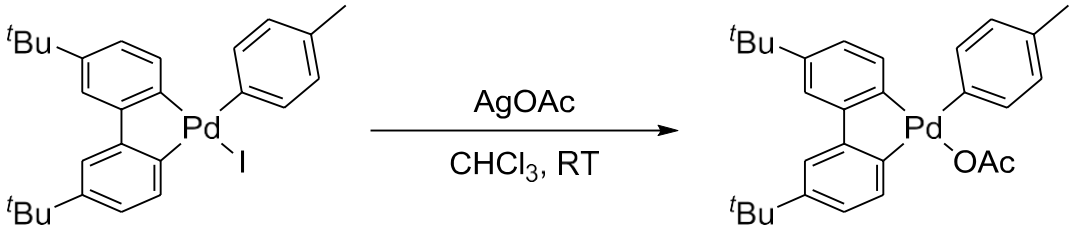


Figure 19. GCMS Spectrum of Commercial Ph-NHAc.

Table 9. Abundance of m/z 135 to 144 for PhNHAc from reaction in presence of AcOH-D_4 vs. independently synthesized.

m/z	Relative Abundance	
	Commercial PhNHAc	PhNHAc formed in reaction in presence of AcOH-D_4
135	90.69%	85.09%
136	8.60%	12.86%
137	0.61%	1.34%
138	0.04%	0.14%
139	0.00%	0.05%
141	0.03%	0.00%
142	0.01%	0.00%
143	0.01%	0.00%
143	0.02%	0.00%
144	0.00%	0.05%

Preparation of (^{t}Bu$_2$bipy)Pd(tol)(OAc) (11)



(^{t}Bu$_2$bipy)Pd(tol)(OAc) was prepared in analogy to the known synthesis of (^{t}Bu$_2$bipy)Pd(Ph)(OAc).[25]

In a nitrogen-filled glovebox, (^{t}Bu$_2$bipy)Pd(tol)(I)[26] (150 mg, 0.25 mmol, 1.00 eq.), AgOAc (120 mg, 0.72 mmol, 2.87 eq.), and 5 mL of $CHCl_3$ were added to a 20 mL scintillation vial, which was sealed with a Teflon-lined vial cap. After stirring at room temperature for 20 min, the mixture was filtered through celite. The collected filtrate was dried under vacuum to yield (^{t}Bu$_2$bipy)Pd(tol)(OAc) (120 mg, 0.23 mmol, 92%) as a yellow solid, which was stored under inert atmosphere.

^{1}H NMR (400 Mz, $CDCl_3$, 25 ºC): δ = 8.45 (m, 1H; bipy), 8.10 (m, 1H; bipy), 7.91 (m, 2H; bipy), 7.51 (m, 1H; bipy), 7.39 (m, 2H; tolArH), 7.24 (m, 1H; bipy), 6.90 (m, 2H; tolArH), 2.30 (s, 3H, tol(CH_3)), 2.08 (s, 3H, OCOCH_3), 1.41 (s, 9H; ^{t}Bu), 1.37 ppm (s, 9H; ^{t}Bu).

[25] Y.-T. Tsoi, Z. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett*. **2010**, 12, 4506.

[26] (^{t}Bu$_2$bipy)Pd(tol)(I) was prepared according to the following reference: Nicholas D. Ball, Jeff W. Kampf, Melanie S. Sanford. *J. Am. Chem. Soc.*, **2010**, *132*, 2878–2879.

^{13}C NMR (400 Mz, $CDCl_3$, 25 ºC): δ = 177.89 (CO), 163.64 (bipy), 163.13 (bipy), 156.63 (bipy), 153.37 (bipy),152.58 (bipy),149.02 (bipy), 148.45 (tolAr), 134.73 (tolAr), 132.60 (tolAr), 127.83(tolAr), 123.74 (bipy), 123.63 (bipy), 118.44 (bipy), 117.76 (bipy), 35.52 ($C(CH_3)_3$), 35.45 ($C(CH_3)_3$), 30.56 ($C(CH_3)_3$), 30.40 ($C(CH_3)_3$), 24.36 ($OCOCH_3$), 21.01 ppm ($tol(CH_3)$).

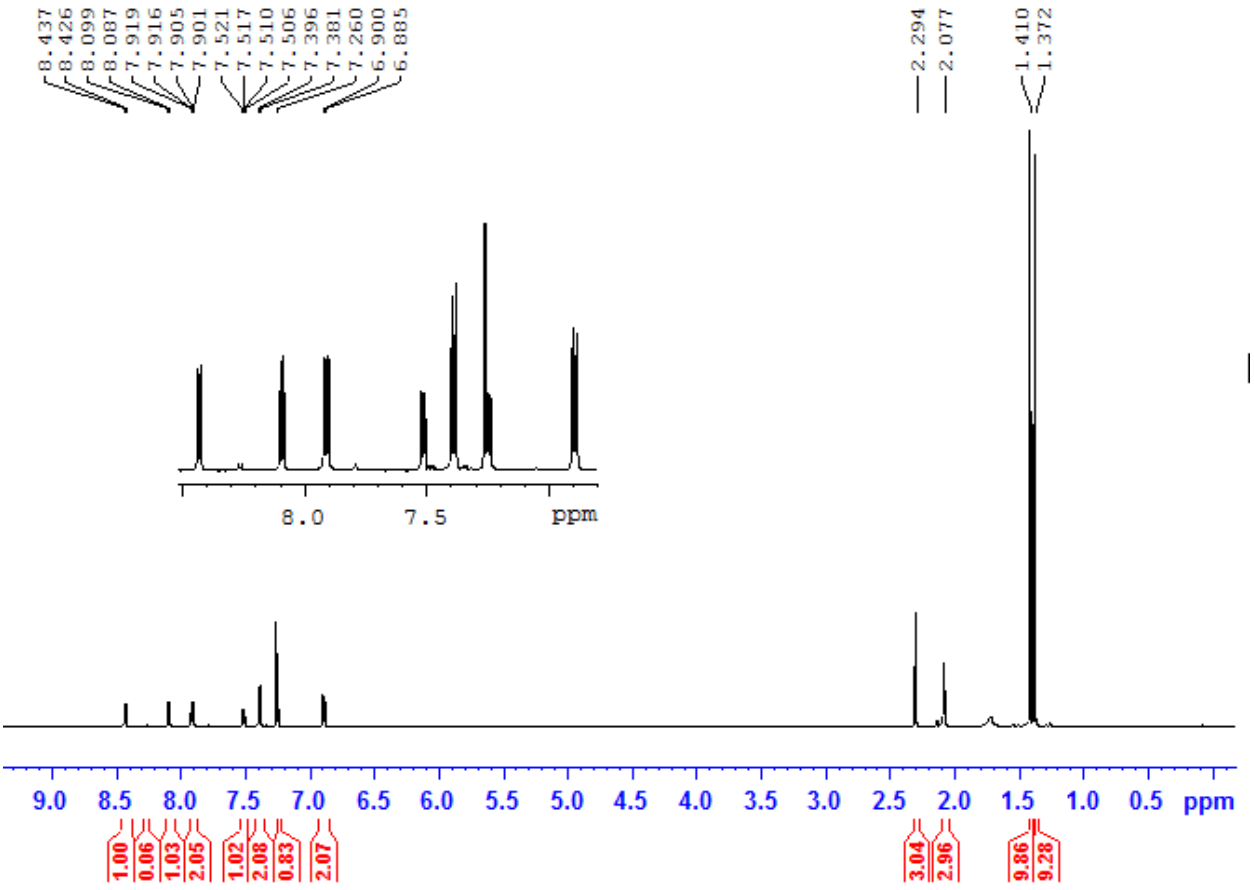


Figure 20. ^{1}H NMR Spectrum of (^{t}Bu$_2$bipy)Pd(tol)(OAc) in $CDCl_3$.

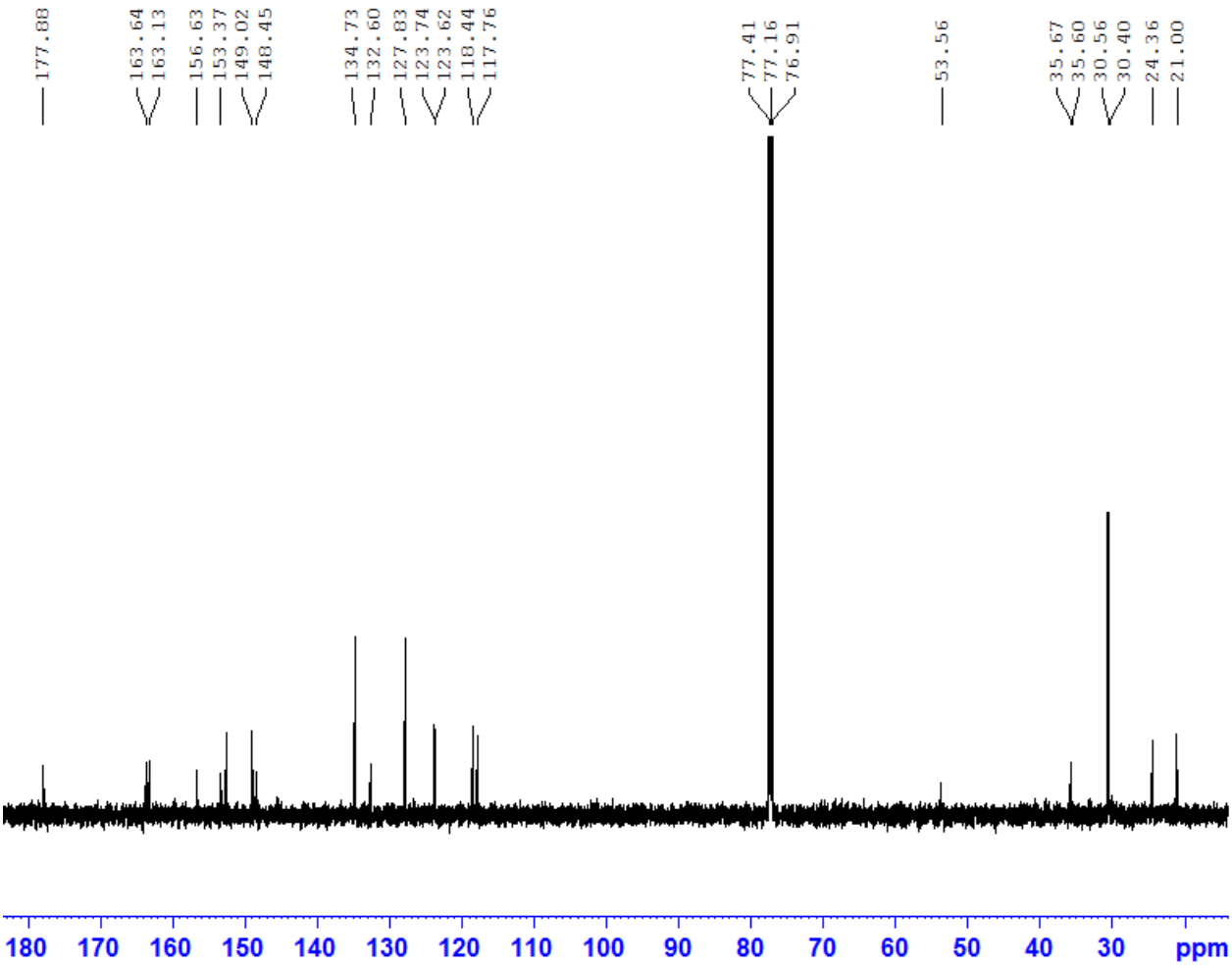
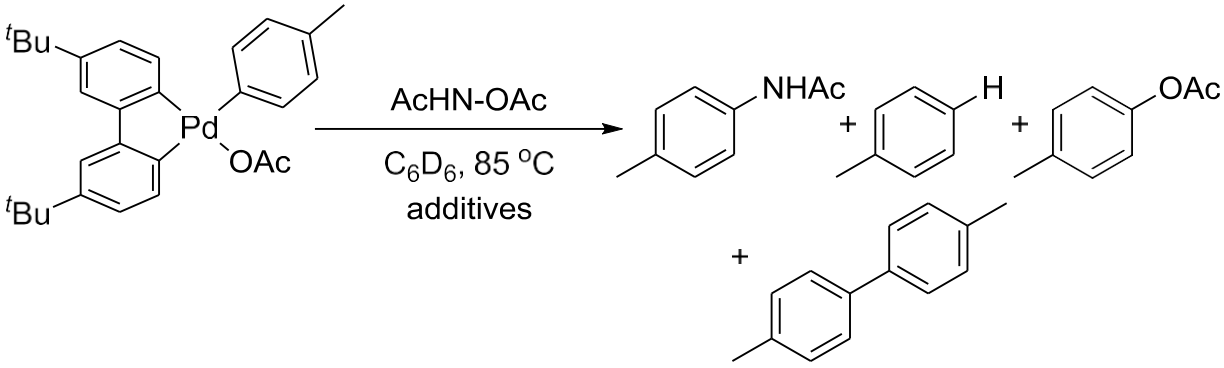


Figure 21. ^{13}C NMR Spectrum of (^{t}Bu$_2$bipy)Pd(tol)(OAc) in CDCl$_3$.

Reactions between (^{t}Bu$_2$bipy)Pd(tol)(OAc) (11) and AcO-NHAc



(^{t}Bu$_2$bipy)Pd(tol)(OAc) (10 mg, 0.019 mmol, 1.0 eq), AcNHOAc (2.3 mg, 0.019 mmol, 1.0 eq), additives (as indicated below; see Table 10), and 1.0 mL of C_6D_6 were added to a scintillation vial. The vial was sealed with a Teflon-lined cap, placed on a preheated heating block and stirred at 85 ºC for 24 h. The reaction was allowed to cool to room temperature and 100 µl of a standard solution of 1,3-dinitrobenzene (100 mg of 1,3-dinitrobenzene in 10 ml of $CDCl_3$; corresponding to 0.006 mmol, 0.31 equiv. of 1,3-dinitrobenzene) was added as internal NMR standard. The resulting mixture was filtered through celite. The yields of toluene, 4,4'-dimethylbiphenyl, 4-methylacetanilide and *p*-tolyl acetate formed were determined by quantitative NMR analysis (NS = 32, d1 = 15 s). Furthermore, GCMS was conducted to confirm the identities of the products. Pd black precipitation was absent in all of these stoichiometric reactions.

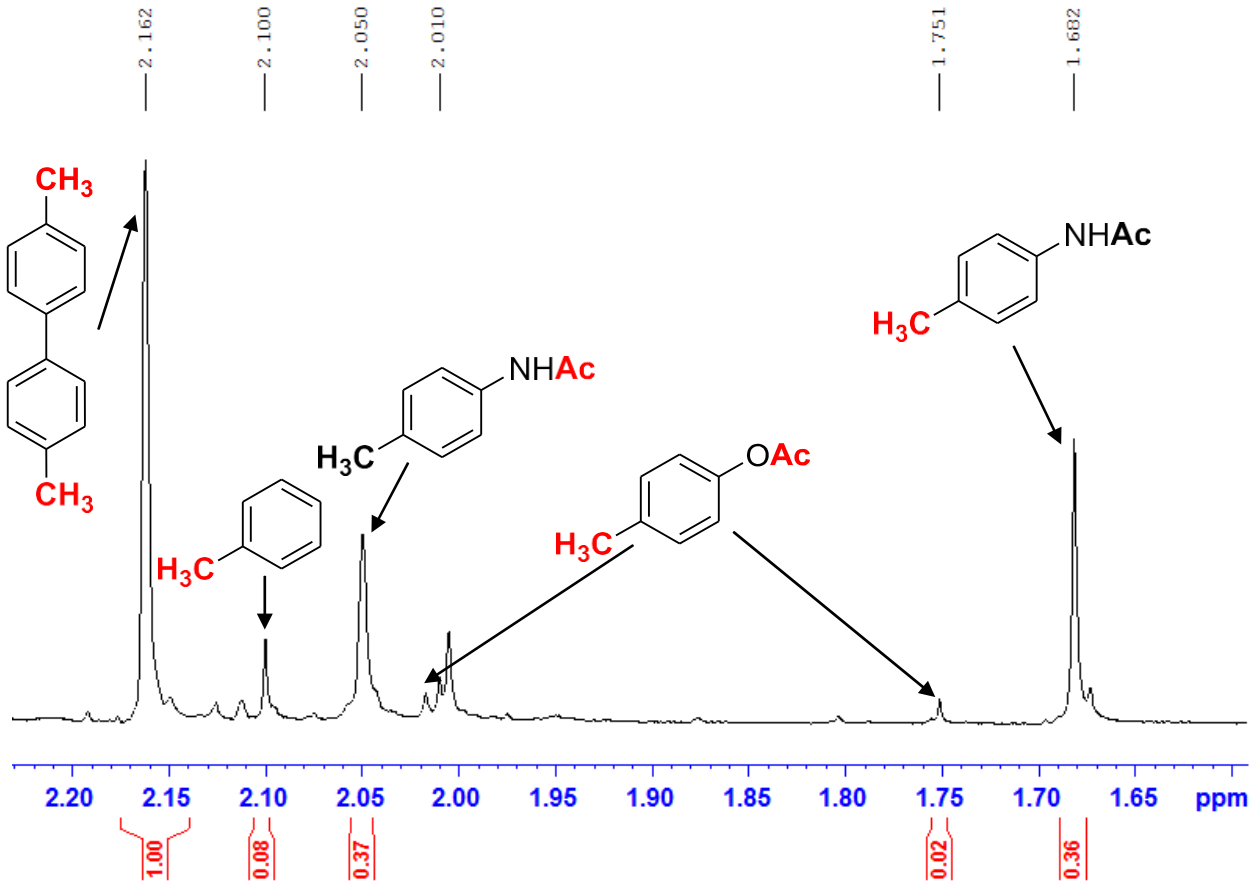
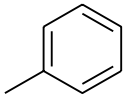
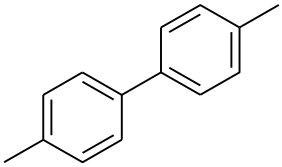
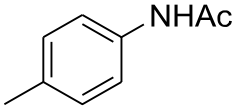
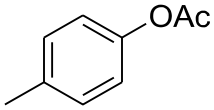


Figure 22. Example of ^{1}H NMR spectrum used to determine product yields.

Table 10. Reactivity of Isolated Pd-Aryl Complex in Presence of Different Additives.

10 eq.

Products \ Additives	None	10 eq AcOH	1 eq C_5F_5N	1 eq AgOAc
	5%	2.5%	3.8%	5%
	32%	6.6%	22%	32.5%
	0%	0%	14%	6.6%
	< 1%	0%	< 1%	< 1%

Amination Reagent Scope

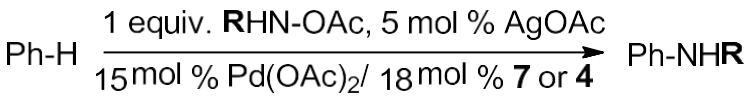
In analogy to the best conditions established above, benzene (0.75 mL, 660 mg, 8.4 mmol, 60 equiv.), $Pd(OAc)_2$ (4.7 mg, 21 mmol, 15 mol %), AgOAc (1.2 mg, 7.0 mmol, 5.0 mol %), ligand **7** (5.4 mg, 25 mmol, 18 mol %) and amination reagent (140 μmol, 1.0 equiv) were added to a scintillation vial (5 mL). The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. The reaction was allowed to cool to room temperature. Product yields were determined by calibrated GC or ^{1}H NMR analysis and are tabulated in Table 11.

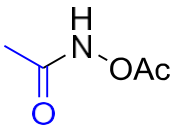
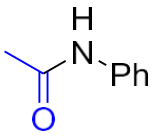
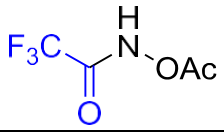
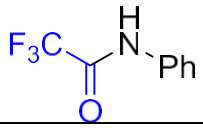
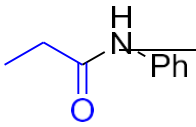
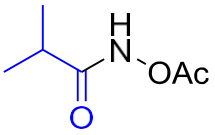
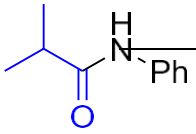
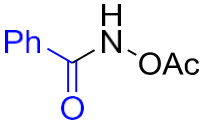
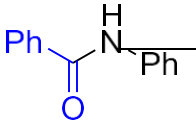
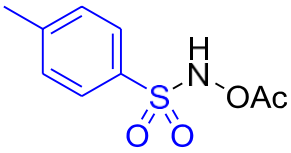
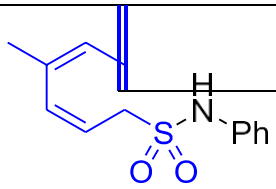
Product Analysis by NMR (for synthesis of PhNHAc, PhNHC(=O)Et, PhNHC(=O)^{i}Pr, and PhNHC(=O)Ph): 0.50 mL (corresponding to 5.0 mg; 29 μmol of 1,3-dinitrobenzene) of a standard solution containing NMR solvent and 1,3-dinitrobenzene as NMR standard (50 mg; 290 μmol in 5.0 mL of $CDCl_3$) were added to the reaction mixture after most of the solvent (benzene) had been removed by applying oil-pump-vacuum. The resulting solution was filtered through celite. The amount of product formed was determined by integration of the ^{1}H NMR signals at 8.97 ppm (1H, 1,3-dinitrobenzene) and 2.21 ppm (3H, PhNHC(O)$\underline{CH_3}$), 3.56 ppm (2H, PhNHC(=O)$\underline{CH_2}CH_3$), 1.14 ppm (6H, PhNHC(=O)CH$\underline{(CH_3)_2}$), or 7.41 ppm (2H, PhNHC(=O)$\underline{C_6H_5}$) (relaxation time = 15.0 s, NS = 16). PhOAc yields were obtained by integrating their ^{1}H NMR signals at 2.32 ppm (3H, PhOC(O)$\underline{CH_3}$) and Ph-Ph yields were obtained from GC with PhCl as internal standard, respectively. All products were additionally identified by GCMS in the reaction mixture and by comparison of the obtained ^{1}H NMR data to the ^{1}H NMR spectra of independently obtained, identical product.

Product Analysis by GC (for synthesis of $PhNHC(O)CF_3$): 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL saturated, aqueous K_2CO_3 solution. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. The amount of product formed was determined by calibrated GC analysis.

Product Analysis by GC (for synthesis of PhNHTs): 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL deionized water. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. The amount of product formed was determined by calibrated GC analysis.

Table 11. NMR/GC Yields of Acylanilines with Different Amination Reagents. Conditions: benzene (60 equiv), $Pd(OAc)_2$ (15 mol %), ligand **7** or **4** (18 mol %) and amination reagent (140 μmol, 1.0 equiv), 100 °C, 24 h.



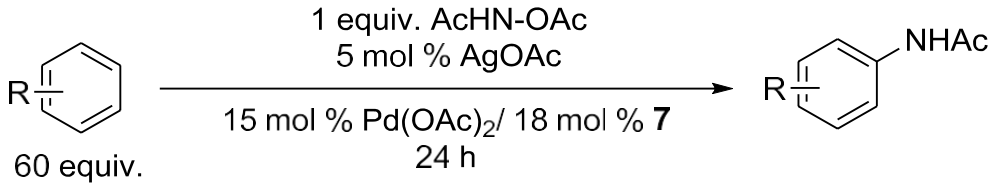
Amination Reagent	Product	Yield	Byproducts (Yield)
		52 ± 3%[a]	Ph-Ph (7 ± 2%) PhOAc (3± 1%)
		53 ± 2%[b]	Ph-Ph (8 ± 2%) PhOAc (5± 1%)
		14 ± 2%[a]	Ph-Ph (12 ± 1%) PhOAc (3± 1%)
		11 ± 2%[a,c]	Ph-Ph (25 ± 1%) PhOAc (5 ± 2%)
		3 ± 0%[a]	Ph-Ph (1 ± 0%) PhOAc (1 ± 0%)
		2 ± 1%[a,c]	Ph-Ph (8 ± 2%) PhOAc (1 ± 1%)
		6 ± 0%[a]	Ph-Ph (8.0 ± 0.3%) PhOAc (5 ± 1%)
		8 ± 1%[a,c]	Ph-Ph (36 ± 1%) PhOAc (8 ± 1%)
		22 ± 2%[a]	Ph-Ph (7± 1 %) PhOAc (7± 2%)
		8 ± 2%[a,c]	Ph-Ph (0%) PhOAc (1 ± 0%)

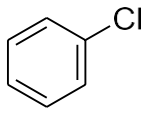
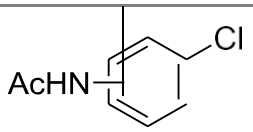
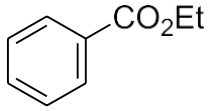
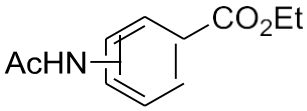
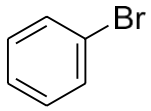
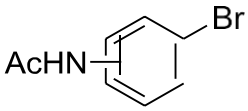
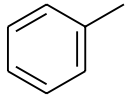
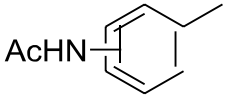
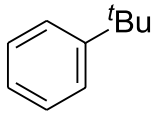
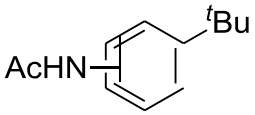
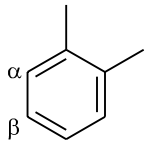
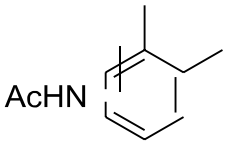
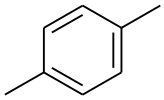
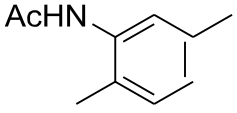
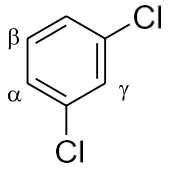
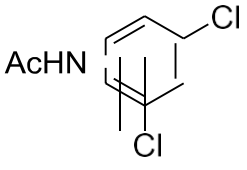
[a]Analysis by 1H NMR. [b]Analysis by calibrated GC/FID. [c]18 mol % quinoline (**4**) was used.

Arene Substrate Scope

In analogy to the best conditions established above, arene (60 equiv.), palladium acetate (4.7 mg, 21 mmol, 15 mol %), ligand **7** (5.4 mg, 25 mmol, 18 mol %) and amination reagent (140 μmol, 1.0 equiv) were added to a scintillation vial (5 mL). The vessel was sealed with a Teflon-lined vial cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. The reaction was allowed to cool to room temperature. 10 μL of PhCl (GC standard) were added, followed by addition of 10 mL of EtOAc and 5 mL saturated, aqueous K_2CO_3 solution. The mixture was thoroughly shaken and the organic layer was separated and filtered through celite. Product yields were determined by calibrated GC analysis and are tabulated in Table 12.

Table 12. Yields of Acylanilines with AcNHOAc/F_3CCONH-OAc. Conditions: Arene (60 equiv), $Pd(OAc)_2$ (15 mol %), ligand **F** (18 mol %), AgOAc (5 mol %), AcNHOAc (140 μmol, 1.0 equiv), 100 °C, 24 h.



Substrate	Product	Yield	Selectivity
		11 ± 2%	1:2:7 (*o*:*m*:*p*)
		14 ± 2%	1:2:7 (*o*:*m*:*p*)
		12 ± 2%	1:3:7 (*o*:*m*:*p*)
		21 ± 2%	1:3:7 (*o*:*m*:*p*)
		13 ± 3%	1:6:11 (*o*:*m*:*p*)
		17 ± 2%	1:2 (*α*:*β*)
		16 ± 2%	n/a
		15 ± 2%	1:3:0 (*α*:*β*:*γ*)