Supporting Information

Reaction Mechanism of Iodine-Catalyzed Michael Additions

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1 Preparation of Anhydrous HI in Different Solvents

1.1 Synthesis of Anhydrous HI

Anhydrous HI is prepared by a procedure of Nanaie and Taylor.[S1] The employed setup is depicted in Figure S1. All connections were sealed with pyrophosphoric acid instead of grease and an argon atmosphere was used for the generation of HI. Initially, pyrophosphoric acid was prepared by slowly heating P_4O_{10} (50.0 g, 176 mmol) and aqueous H_3PO_4 85 wt% (50.0 mL) while purging the apparatus with argon (argon stream from **B** to **A** and to the atmosphere). After a homogeneous solution was obtained, the mixture was allowed to cool to room temperature and all cooling traps were filled with *i*PrOH/dry ice. Next, KI (7.0 g, 42 mmol) was added to the pyrophosphoric acid and the mixture was slowly heated (not higher than 100 °C). The formed HI was collected in the first cooling trap. Successive distillation of HI to the last cooling trap in an argon atmosphere gave pure and colorless HI which can be transferred via a Teflon cannula into a degassed solvent.

Figure S1: Experimental setup for the synthesis of anhydrous HI.

1.2 Potentiometric Titration of HI

The concentration of anhydrous HI in different organic solvents has been determined by adding a small amount of HI solution to ~30 mL of degassed acetone under argon atmosphere. The solution was titrated with pure NEt_3 while the conductivity of the solution was monitored. This procedure was used prior to any reaction with anhydrous HI. Representative examples are given in Table S1 and Table S2.

Table S1: Titrations of a Solution of HI in Toluene (in Acetone with NEt_3).

Measurement	$V_{\text{HI in toluene}}$ [mL]	V_{Et3N} [μL]	$c_{\text{HI in toluene}}$ [mM]
1	5.00	30.3	43.4
2	5.00	29.5	42.3
3	5.00	34.2	49.0
Average c(HI in toluene) = 45 ± 3 mM			

Table S2: Titrations of a Solution of HI in Dichloromethane (in Acetone with NEt_3)

Measurement	$V_{\text{HI in DCM}}$ [mL]	V_{Et3N} [μL]	$c_{\text{HI in DCM}}$ [mm]
1	10.0	152	109
2	5.00	72.8	104
Average c(HI in CH_2Cl_2) = 107 ± 3 mM			

2 HPLC Calibration

2.1 Linear Behavior of the Absorption

A stock solution of Ph_2O (68.9 mg, 205 μmol) in *i*PrOH was prepared in a volumetric flask (100 mL). Based on this stock solution, five samples with Ph_2O concentrations between 0.6 and 3.1 mmol L^{-1} were prepared and analyzed by HPLC. Table S3 summarizes the determined UV absorption at 223 nm, while Figure S2 displays a linear correlation between the determined integrals and the employed standard concentrations. This indicates that the HPLC integral correlates linearly with the standard concentration within the concentration range.

Table S3: Solutions and HPLC Integral (223 nm) for Ph_2O at Different Concentrations.

$V(Ph_2O)$ [mL]	V_{tot} [mL]	$c(Ph_2O)$ [mM]	$I(Ph_2O)$
1.60	10.0	0.65	1.72×10^6
3.00	10.0	1.21	3.33×10^6
4.60	10.0	1.86	4.96×10^6
6.00	10.0	2.43	6.49×10^6
7.60	10.0	3.08	8.09×10^6

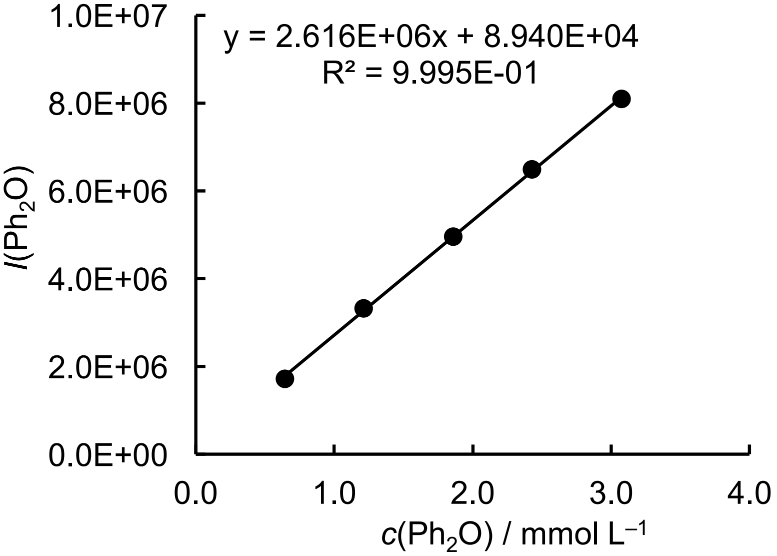


Figure S2: Correlation between the employed concentration and the HPLC integral *I* for Ph_2O.

2.2 Determination of Calibration Lines

In order to interconvert the observed HPLC integrals to concentrations, we have determined calibration lines for both starting materials – *trans*-crotonophenone (**3**) and indole (**4**) – as well as for the product **5**. For this purpose, three different stock solutions containing either Ph_2O, an approximately 1:1 mixture of **3** and **4**, or **5** have been prepared in volumetric flasks. Based on these stock solutions, eight samples covering a ratio of 0.23–3.05 (for each of **3**, **4**, and **5** to the internal standard Ph_2O) in a concentration range of 0.5 – 3.6 mmol L^{-1} have been prepared. For the HPLC analysis, a detection wavelength of 223 nm for all species was used.

Typical retention times for all species are as follows:
R_t [Ph_2O] = 4.7 min
R_t [**3**] = 6.7 min
R_t [**4**] = 15.7 min
R_t [**5**] = 21.7 and 35.5 min for both enantiomers.

The data summarized in Table S4 have been used for the correlation analysis depicted in Figure S3. The correlation equations based on least-squares fits were subsequently used to calculate the actual concentrations of all species in solution.

Table S4: Calibration Solutions and HPLC Integrals (*I*, at 223 nm) for all Compounds.

V(Ph_2O) [μL]	*V*(**3**+**4**) [μL]	*V*(**5**) [μL]	V_{tot} [μL]	*c*(Ph_2O) [mM]	*c*(**3**) [mM]	*c*(**4**) [mM]	*c*(**5**) [mM]	*I*(Ph_2O)	*I*(**3**)	*I*(**4**)	*I*(**5**)[a]
50	10	110	160	1.18	0.33	0.28	3.16	3.83×10^6	7.35×10^5	2.17×10^6	3.69×10^7
50	30	90	160	1.18	0.99	0.83	2.59	3.65×10^6	2.00×10^6	5.82×10^6	2.89×10^7
50	50	70	160	1.18	1.64	1.38	2.01	3.56×10^6	3.23×10^6	9.28×10^6	2.18×10^7
50	70	50	160	1.18	2.30	1.93	1.44	3.50×10^6	4.44×10^6	1.26×10^6	1.54×10^7
50	90	30	160	1.18	2.96	2.48	0.86	3.44×10^6	5.61×10^6	1.57×10^6	9.04×10^6

[a]: for both enantiomers of **5**.

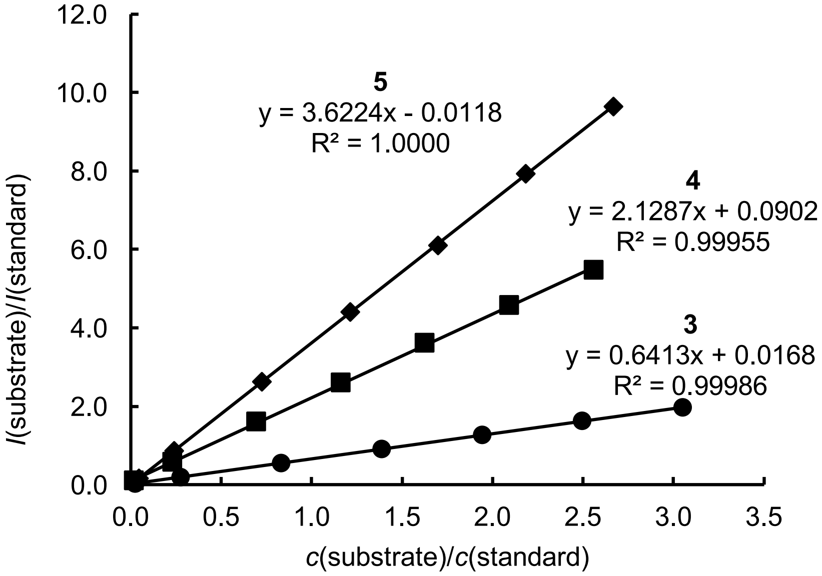
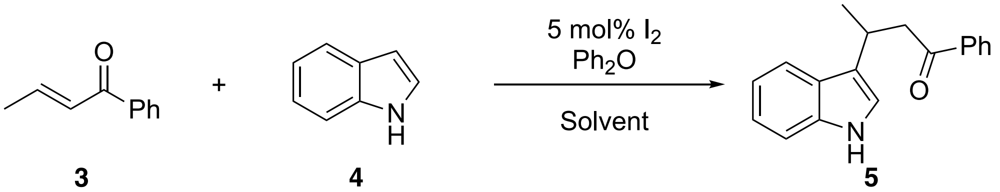


Figure S3: Correlation between the relative concentrations and the relative HPLC integrals *I* (at 223 nm) for **3**, **4**, and **5**.

3 Solvent Effects on the Iodine-Catalyzed Reaction of Indole (4) and *trans*-Crotonophenone (3)



The electrophile **3** was dissolved in the desired solvent and a solution of indole (**4**) and Ph_2O in the desired solvent was added at 23 °C. The reaction was started by addition of an iodine solution resulting in the following concentrations in the reaction mixture: [**3**] ≈ [**4**] = 0.50 M, [Ph_2O] = 0.25 M, [I_2] = 25 mM. The deactivating agent has been prepared by adding water (25 mL) to a mixture (ca 2.7 g) containing silica (80 wt%), $Na_2S_2O_3$ (10 wt%), and Na_2CO_3 (10 wt%). After removal of water under reduced pressure and elevated temperature, a highly reactive deactivation agent was obtained which effectively decolorizes iodine solutions during filtration. After 3 minutes, a pipette is used to take a sample (~20–50 µL), and the sample is transferred with *i*-propanol (2 mL) to a small column charged with cotton and the deactivation agent. After elution with additional *i*-propanol (8 mL), the filtrate was used for HPLC measurements. Content of product **5** was quantified by its ratio to the internal standard and the HPLC yields in different solvents are given in Table S5.

Table S5: Experimental Details for the Iodine-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) in Various Solvents (23 °C).

Entry	Solvent	**3**	**4**	Ph_2O	I_2	V_{total} [mL]	Yield
1	THF	58.9 mg (403 µmol)	46.9 mg (400 µmol)	35.1 mg (206 µmol)	5.0 mg (20 µmol, 5.0 mol-%)	0.80	90 %
2	1,4-Dioxane	64.2 mg (439 µmol)	51.5 mg (440 µmol)	37.5 mg (220 µmol)	5.6 mg (22 µmol, 5.0 mol-%)	0.87	89 %
3	Et_2O	64.5 mg (441 µmol)	51.4 mg (439 µmol)	37.3 mg (219 µmol)	5.6 mg (22 µmol, 5.0 mol-%)	0.88	82 %
4	*t*BuOMe	64.3 mg (440 µmol)	51.4 mg (439 µmol)	37.3 mg (219 µmol)	5.7 mg (22 µmol, 5.1 mol-%)	0.88	82 %
5	$ClCH_2CH_2Cl$	63.3 mg (433 µmol)	50.3 mg (429 µmol)	36.6 mg (215 µmol)	5.3 mg (21 µmol, 4.9 mol-%)	0.85	80 %
6	EtOAc	58.5 mg (400 µmol)	50.1 mg (428 µmol)	38.8 mg (228 µmol)	5.0 mg (20 µmol, 4.9 mol-%)	0.83	79 %
7	CH_2Cl_2	69.3 mg (474 µmol)	55.0 mg (470 µmol)	40.0 mg (235 µmol)	6.0 mg, (24 µmol, 5.1 mol-%)	0.94	76 %
9	C_6H_6	59.4 mg (406 µmol)	47.5 mg (405 µmol)	34.6 mg (203 µmol)	5.1 mg (20 µmol, 5.0 mol-%)	0.81	70 %
10	Toluene	54.6 mg (374 µmol)	43.3 mg (370 µmol)	31.5 mg (185 µmol)	4.7 mg (19 µmol, 5.1 mol-%)	0.73	67 %
11	$CHCl_3$	58.2 mg (398 µmol)	46.9 mg (400 µmol)	35.1 mg (206 µmol)	5.1 mg (20 µmol, 5.0 mol-%)	0.80	59 %

Entry	Solvent	**3**	**4**	Ph_2O	I_2	V_{total} [mL]	Yield
12	CCl_4	60.3 mg (413 µmol)	48.0 mg (410 µmol)	35.0 mg (206 µmol)	5.1 mg (20 µmol, 4.9 mol-%)	0.82	55 %[a]
13	CH_3OH	64.2 mg (439 µmol)	51.6 mg (440 µmol)	38.6 mg (227 µmol)	5.6 mg (22 µmol, 5.0 mol-%)	0.88	33 %
14	*i*PrOH	66.6 mg (456 µmol)	52.7 mg (450 µmol)	38.4 mg (226 µmol)	5.78 mg (23 µmol, 5.1 mol-%)	0.91	7 %
15	DMSO	53.8 mg (368 µmol)	43.3 mg (370 µmol	31.5 mg (185 µmol)	4.7 mg (19 µmol, 5.1 mol-%)	0.74	0 %
16	DMF	65.0 mg (445 µmol)	51.5 mg (440 µmol)	37.3 mg (219 µmol)	5.6 mg (22 µmol, 5.0 mol-%)	0.88	0 %

[a] not a homogeneous solution.

4 HI- and I_2-Catalysis in Different Solvents

4.1 General Procedure for HPLC Analysis

A solution of indole (**4**), *trans*-crotonophenone (**3**), and diphenyl ether was added to a solution of the catalyst in the desired solvent at 23 °C. This results in a reaction mixture approx. 0.50 M in each substrate and approx. 0.25 M in diphenyl ether. Catalyst solutions were titrated prior to each use (aqueous HI with NaOH and methylene red as indicator; anhydrous HI potentiometric with NEt_3). The catalyst concentration varied in each solvent due to the different solubility of HI in these solvents (CH_3CN, 5 mol%; CH_2Cl_2, 3 mol%; toluene, 2 mol%). The same work-up procedure and HPLC analysis has been used as described above. Table S6 and Table S7 summarize the individual experiments in different solvents.

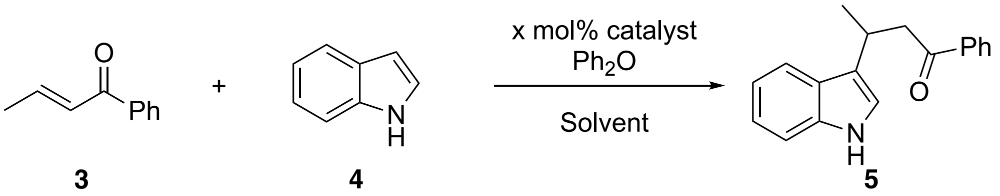


Table S6: Experimental Details for the Iodine-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) in Various Solvents (23 °C; Ph_2O as Internal Standard).

Entry	**3**	**4**	Ph_2O	Catalyst	Solvent	V_{total} [mL]	HPLC Yield
1	43.9 mg (300 µmol)	35.1 mg (300 µmol)	5.1 mg (30 µmol)	I_2 (3.8 mg 15 µmol, 5.0 mol%)	CH_3CN	0.60	91 %
2	43.9 mg (300 µmol)	35.1 mg (300 µmol)	25.5 mg (150 µmol)	I_2 (3.8 mg 15 µmol, 5.0 mol%)	CH_3CN	0.60	97 %
3	43.9 mg (300 µmol)	35.1 mg (300 µmol)	38.3 mg (225 µmol)	I_2 (3.8 mg 15 µmol, 5.0 mol%)	CH_3CN	0.60	92 %
4	72.8 mg (498 µmol)	58.0 mg (495 µmol)	47.1 mg (277 µmol)	I_2 (3.8 mg, 15 µmol, 3.0 mol%)	CH_2Cl_2	1.00	72 %
5	117 mg (801 µmol)	94.0 mg (802 µmol)	65.6 mg (386 µmol)	I_2 (4.4 mg, 18 µmol, 2.2 mol%)	Toluene	0.80	60 %

Average HPLC yield for iodine catalysis in CH_3CN: 93 ± 3 %

Table S7: Experimental Details for the HI-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) in Various Solvents (23 °C; Ph_2O as Internal Standard).

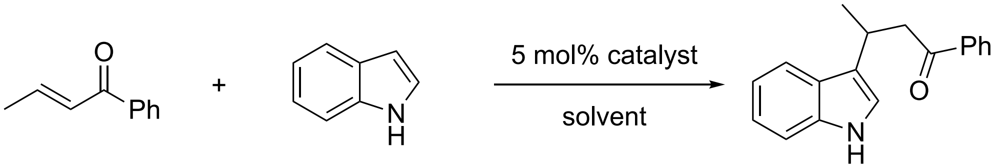
Entry	**3**	**4**	Ph_2O	Catalyst	Solvent	V_{total} [mL]	HPLC Yield
1	43.9 mg (300 µmol)	35.1 mg (300 µmol)	5.1 mg (30 µmol)	HI (1.9 mg, 15 µmol 5.0 mol%)	CH_3CN[a]	0.45	61 %
2	43.9 mg (300 µmol)	35.1 mg (300 µmol)	25.5 mg (150 µmol)	HI (1.9 mg, 15 µmol 5.0 mol%)	CH_3CN[a]	0.45	60 %
3	43.9 mg (300 µmol)	35.1 mg (300 µmol)	38.3 mg (225 µmol)	HI (1.9 mg, 15 µmol 5.0 mol%)	CH_3CN[a]	0.45	53 %
4	72.8 mg (498 µmol)	58.0 mg (495 µmol)	47.1 mg (277 µmol)	HI (1.8 mg, 14 µmol, 2.9 mol%)	CH_2Cl_2	1.00	34 %
5	117 mg (801 µmol)	94.0 mg (802 µmol)	65.6 mg (386 µmol)	HI (2.3 mg, 18 µmol, 2.2 mol%)	Toluene	0.80	17 %

[a]: contains 1.4 mg (78 µmol) water

Average HPLC yield for HI catalysis in CH_3CN: 58 ± 3 %

4.2 General Procedure for Isolated Products in CH_3CN

A solution of *trans*-crotonophenone (**3**) and indole (**4**) was added to a solution of the catalyst in the desired solvent at 23 °C. This results in a reaction mixture approx. 0.50 M in each substrate and approx. 0.25 M in diphenyl ether. The HI was titrated prior to each use (aqueous HI with 0.1 M NaOH and methylene red as an indicator). The catalyst concentration in CH_3CN was approx. 25 mM. After 3 minutes, ca 1 mL of a deactivating solution (1:1 (*v*/*v*) mixture of saturated aqueous $Na_2S_2O_3$ solution and aqueous NaOH) was added. The mixture was subsequently diluted with ethyl acetate (80 mL) and deactivating solution (~9 mL). The organic layer was washed with water (2 × 10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on SiO_2 (ethyl acetate/*cyclo*-hexane, 1:9 (*v*/*v*)) to give the desired product **5**. Table S8 and Table S9 summarize the individual experiments.



3 **4** **5**

Table S8: Experimental Details for the I_2-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) (CH_3CN, 23 °C).

Entry	**3**	**4**	Catalyst	V_{total} [mL]	Isolated Yield
1	58.4 mg (399 μmol)	46.9 mg (400 μmol)	I_2 (5.0 mg, 20 μmol, 5.0 mol%)	0.80	76.4 mg (290 μmol, 73 %)
2	59.7 mg (408 μmol)	46.9 mg (400 μmol	I_2 (5.1 mg, 20 μmol, 5.0 mol%)	0.80	76.5 mg (290 μmol, 73 %)
3	74.6 mg (510 μmol)	58.6 mg (500 μmol)	I_2 (6.4 mg, 25 μmol, 5.0 mol%)	1.00	101 mg (380 μmol, 77 %)
4	58.4 mg (399 μmol)	47.0 mg (401 μmol)	I_2 (5.1 mg, 20 μmol, 5.0 mol%)	0.80	73.7 mg (280 μmol, 70 %)

Average yield for iodine catalysis in CH_3CN: 73 ± 3 %

Table S9: Experimental Details for the HI-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) (CH_3CN, 23 °C).

Entry	**3**	**4**	Catalyst	V_{total} [mL]	Isolated Yield
1[a]	58.4 mg (399 μmol)	47.0 mg (401 μmol)	HI (2.6 mg, 20 μmol, 5.0 mol%)	0.80	39.5 mg (150 μmol, 37 %)
2[a]	74.6 mg (510 μmol)	58.6 mg (500 μmol)	HI (3.2 mg, 25 μmol, 5.0 mol%)	1.00	57.9 mg (220 μmol, 43 %)
3[a]	58.4 mg (399 μmol)	46.9 mg (400 μmol)	HI (2.6 mg, 20 μmol, 5.0 mol%)	0.80	44.8 mg (170 μmol, 43 %)
4[a]	59.7 mg (408 μmol)	46.9 mg (400 μmol)	HI (2.6 mg, 20 μmol, 5.0 mol%)	0.80	42.1 mg (160 μmol, 39 %)

[a]: contains 1.4 mg (78 μmol) water

Average yield for HI catalysis in CH_3CN: 40 ± 3 %

4.3 Conjugate HI-Addition to the Michael Acceptor 3

The conjugate addition of HI to *trans*-crotonophenone (**3**) might be a putative side reaction.[S2] To check the importance of this reaction for the analysis discussed in this mauscript, stock solutions of *trans*-crotonophenone (**3**) containing tetraethylsilane as the internal standard have been prepared in deuterated acetonitrile. The reaction was started by addition of a titrated solution of aqueous HI (57 wt%) in deuterated acetonitrile. This resulted in approx. 0.50 M concentrations of **3** and HI and 0.25 M for $SiEt_4$ in the NMR tube. The reaction progress was monitored by ^1H NMR spectroscopy and the results are summarized in Figure S4. The conjugate HI addition takes place in a slow reaction (approx. 15 % after 3 min) and less than 40 % conversion can be observed after 2 h.

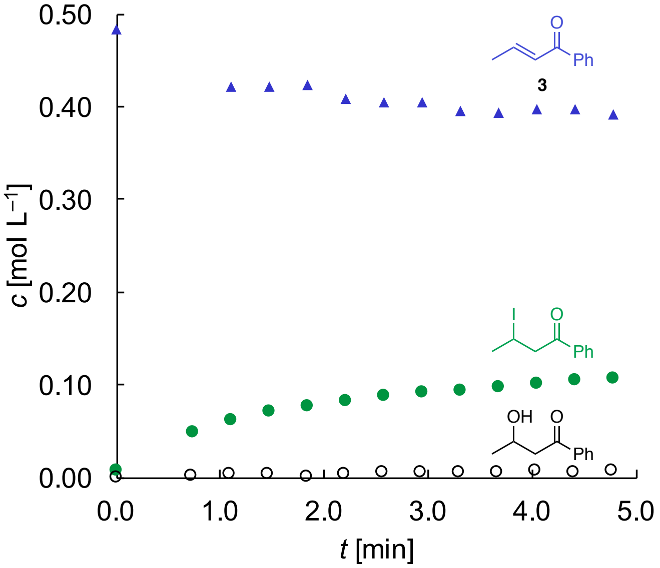


Figure S4: Concentration-time profiles for the reaction of *trans*-crotonophenone (**3**, 0.50 M) and HI (0.50 M) monitored by ^1H NMR spectroscopy using $SiEt_4$ (0.25 M) as an internal standard (CD_3CN, 23 °C).

5 Influence of Additives on I_2- and HI-Catalysis

A solution of *trans*-crotonophenone (**3**) and indole (**4**) was added to a solution of the catalyst and the additive in CH_3CN at 23 °C. This results in a reaction mixture approx. 0.50 M in each substrate and approx. 0.25 M in diphenyl ether. The HI was titrated prior to each use (aqueous HI with 0.1 M NaOH and methylene red as an indicator). The catalyst concentration in CH_3CN was approx. 25 mM. After 3 minutes, ca 1 mL of a deactivating solution (1:1 (*v*/*v*) mixture of saturated aqueous $Na_2S_2O_3$ solution and aqueous NaOH) was added. The mixture was subsequently diluted with ethyl acetate (80 mL) and deactivating solution (~9 mL). The organic layer was washed with water (2 × 10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on SiO_2 (ethyl acetate/*cyclo*-hexane, 1:9 (*v*/*v*)) to give the desired product **5**. Table S10 and Table S11 summarize the details of these experiments.

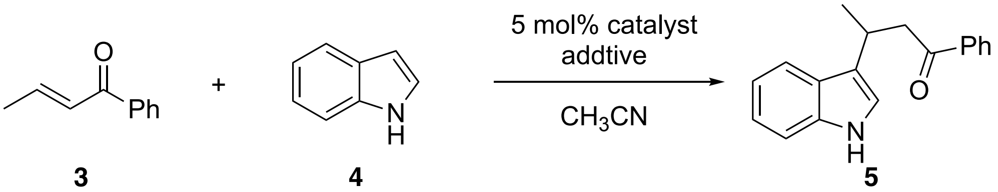


Table S10: Experimental Details for the I_2-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) in the Presence of Additives (CH_3CN, 23 °C).

3	**4**	Catalyst	Additive	V_{total} [mL]	Yield
		Iodine as Catalyst			
58.4 mg (399 µmol)	46.9 mg (400 µmol)	5.0 mg (20 µmol, 5.0 mol%)	none	0.80	76.4 mg (290 µmol, 73 %)
74.6 mg (510 µmol)	58.6 mg (500 µmol)	6.3 mg (25 µmol, 5.0 mol%)	H_2O 2.6 mg (0.14 µmol)	1.00	107 mg (407 µmol, 81 %)
75.0 (513 µmol)	58.5 mg (500 µmol)	6.4 mg (25 µmol, 5.0 mol%)	H_2O 2.4 mg (0.13 µmol)	1.00	79.0 mg (300 µmol, 61 %)
60.0 mg (410 µmol)	46.5 mg (397 µmol)	5.0 mg (20 µmol, 5.0 mol%)	KI 80 mg (0.48 µmol)	0.80	0%[b]
59.1 mg (404 µmol)	46.8 mg (399 µmol)	5.0 mg (20 µmol, 4.9 mol%)	3 Å molecular sieve (119 mg)	0.80	78 %

[a]: contains 1.9 mg (0.11 µmol) water [b]: no product observed in ^1H NMR spectra of the deactivated mixture.

Average yield for iodine catalysis in wet CH_3CN: 71 %

Table S11: Experimental Details for the Acid-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) in the Presence of Additives (CH_3CN, 23 °C).

3	**4**	Catalyst	Additive	V_{total} [mL]	Yield
		HI as Catalyst[a]			
74.6 mg (510 µmol)	58.6 mg (500 µmol)	3.2 mg (25 µmol, 5.0 mol%)	none	1.00	57.9 mg (220 µmol, 43 %)
58.8 mg (402 µmol)	47.0 mg (402 µmol)	2.6 mg (20 µmol, 5.0 mol%)	KI 80 mg (0.48 mmol)	0.80	42.1 mg (160 µmol, 40 %)
60.3 mg (398 µmol)	46.7 mg (398 µmol)	2.6 mg (20 µmol, 5.0 mol%)	3 Å molecular sieve (~50 mg)	0.80	20 mg (76 µmol, 19 %)
59.0 (403 µmol)	47.0 (401 µmol)	2.6 mg (20 µmol, 5.0 mol%)	3 Å molecular sieve (~25 mg)	0.80	20 mg (76 µmol, 19 %)
57.8 mg (395 µmol)	46.7 mg (380 µmol)	2.6 mg (20 µmol, 5.3 mol%)	KI 50 mg (0.30 mmol) 3 Å molecular sieve (~125 mg)	0.80	0 %[b]
		HOTf as Catalyst			
73.2 mg (501 µmol)	59.3 (506 µmol)	4.0 mg (27 µmol, 5.4 mol%)	none	1.00	75.9 mg (290 µmol, 56 %)
60.3 mg (412 µmol)	46.7 mg (398 µmol)	3.0 mg (20 µmol, 5.0 mol%)	3 Å molecular sieve (~50 mg)	0.80	19 mg (72 µmol, 18 %)

[a]: contains 1.9 mg (0.11 µmol) water [b]: no product observed in ^{1}H NMR spectra of the deactivated mixture.

UV spectra support the conclusion that triiodide anions are formed when iodine is combined with KI. The iodine band at 450 nm disappears and the bands for at 290 and 360 nm appear that are characteristic for the triiodide anion (Figure S5).[S3]

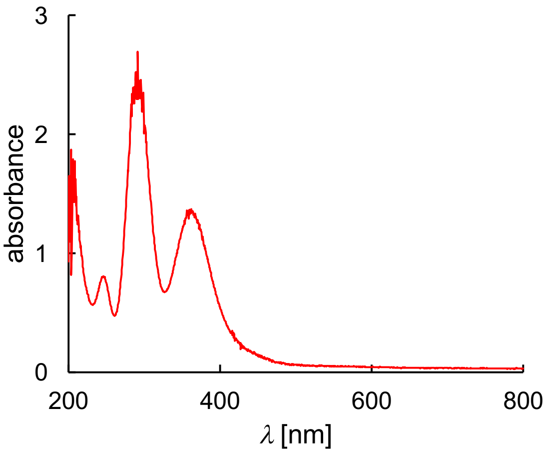
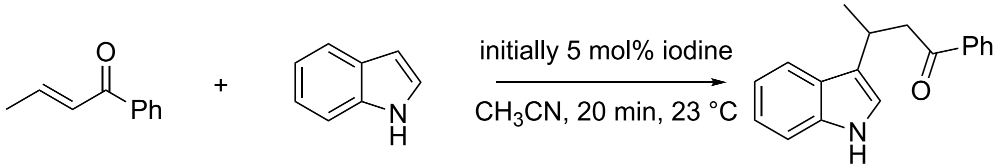


Figure S5: UV-Vis spectrum of an iodine-KI mixture ($[I_2]$ = 50 µmol L^{-1}, [KI] = 50 µmol L^{-1}) In acetonitrile.

6 Performance of Iodine in Several Catalytic Cycles



3 **4** **5**

Experiment A

To 0.40 mL of a solution of iodine (49 mM, 125.3 mg in 10 mL) in acetonitrile, 0.20 mL of a solution containing indole (**4**, 2.0 M, 1172 mg in 5.0 mL) and *trans*-crotonophenone (**3**, 2.0 M, 1461 mg in 5.0 mL) as well as diphenyl ether (1.0 M, 839.8 mg in 5.0 mL) was added. After 20 minutes an HPLC sample was prepared and another 0.20 mL of the same solution was added. This process was repeated 5 times. Reaction times of 20 min per cycle were chosen to ensure that dilution effects are negligible. The results are summarized in Table S12.

Experiment B

In a second experiment the same procedure as described above was performed but after the 2nd cycle potassium iodide (83 mg, 0.50 mmol, 25 eq. compared to iodine) was added and stirred for 20 min before the next cycle started. The results are summarized in Table S13.

Data Processing

HPLC yield and consumption was calculated from the chromatograms using the known concentrations of the internal standard Ph_2O. To calculate the consumption and different yields the following formulas (Eqs S1–S3) have been employed where X is the yield of the last step and Y the total yield over all cycles:

$$Y = \left[\frac{\left[\left[\left(\frac{I_{[Prod]}}{I_{[Stand]}}\right) - intercept_{[Prod\ calibration]}\right]\right]}{slope_{[Prod\ calibration]}}\right] * n_{[Stand]}/n_{0[limiting\ Sub]} \qquad \text{(S1)}$$

$$Y_n = \frac{1}{n}X + \frac{n-1}{n}Y_{n-1} \qquad \text{(S2)}$$

$$X = [n * Y_n] - [(n-1) * Y_{n-1}] \qquad \text{(S3)}$$

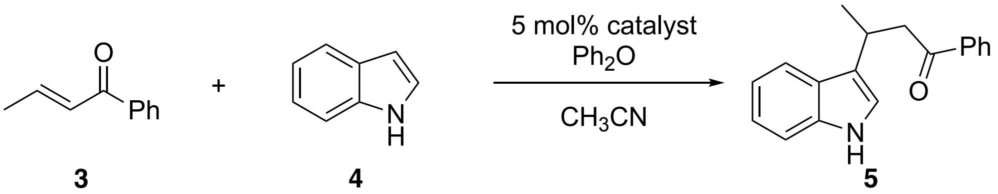
Table S12: Experimental Details for Experiment A.

cycle number	1	2	3	4	5
effective iodine concentration [mol L^{-1}]	0.033	0.025	0.020	0.017	0.014
added substrate volume [mL]	0.20	0.20	0.20	0.20	0.20
total volume [mL]	0.60	0.80	1.00	1.20	1.40
total yield [sum of product]	87 %	80 %	79 %	88 %	77 %
yield in this step	87 %	74 %	76 %	72 %	78 %

Table S13: Experimental Details for Experiment B.

cycle number	1	2	KI Addition	3	4
effective iodine concentration [mol L^{-1}]	0.032	0.024		0.019	0.016
added substrate volume [mL]	0.20	0.20		0.20	0.20
total volume [mL]	0.61	0.82		1.01	1.21
total yield [sum of product]	93 %	87 %	86 %	58 %	44 %
yield in this step	93 %	81 %	-	2 %	4 %

7 Comparison with other Lewis Acids



A solution of *trans*-crotonophenone (**3**), indole (**4**), and diphenyl ether was added to a solution of the catalyst in acetonitrile at 23 °C. This results in a reaction mixture approx. 0.50 M in each substrate approx. 0.13 M in diphenyl ether and approx. 0.025 M in the catalyst (5.0 mol%). The same work-up procedure and HPLC analysis has been used as described above. The results are summarized in Table S14.

Table S14: HPLC Yields for the Lewis-Acid-Catalyzed Reaction between *trans*-Crotonophenone (**3**) and Indole (**4**) (CH_3CN, 23 °C).

3	**4**	Ph_2O	Catalyst	V_{total} [mL]	Yield
30.0 mg (205 µmol)	25.0 mg (213 µmol)	8.85 mg (52.0 µmol)	$TiCl_4$ 1.90 mg (10.0 µmol, 4.9 mol%)	0.40	96 %
90.8 mg (621 µmol)	71.7 mg (612 µmol)	29.5 mg (173 µmol)	$TiCl_4$ 1.16 mg (6.12 µmol, 1.0 mol%)	1.22	33 %
30.0 mg (205 µmol)	25.0 mg (213 µmol)	8.85 mg (52.0 µmol)	$AlCl_3$ 1.48 mg (11.1 µmol, 5.4 mol%)	0.40	90 %
90.1 mg (616 µmol)	71.7 mg (612 µmol)	29.5 mg (173 µmol	$AlCl_3$ 0.82 mg (6.2 µmol, 1.0 mol%	1.22	28 %
30.0 mg (205 µmol)	25.0 mg (213 µmol)	8.85 mg (52.0 µmol)	$CuBr_2$ 2.25 mg (10.1 µmol, 4.9 mol%)	0.40	47 %
30.0 mg (205 µmol)	25.0 mg (213 µmol)	8.85 mg (52.0 µmol)	$FeCl_3$: 1.71 mg (10.5 µmol, 5.1 mol%)	0.40	19 %
30.0 mg (205 µmol)	25.0 mg (213 µmol)	8.85 mg (52.0 µmol)	$InCl_3$ 2.43 mg (11.0 µmol, 5.4 mol%)	0.40	8 %
83.2 mg (569 µmol)	65.9 mg (563 µmol)	27.1 mg (159 µmol)	I_2 1.43 mg (5.63 µmol, 1.0 mol%)	1.13	41 %

8 Kinetic Analysis using IR Spectroscopy

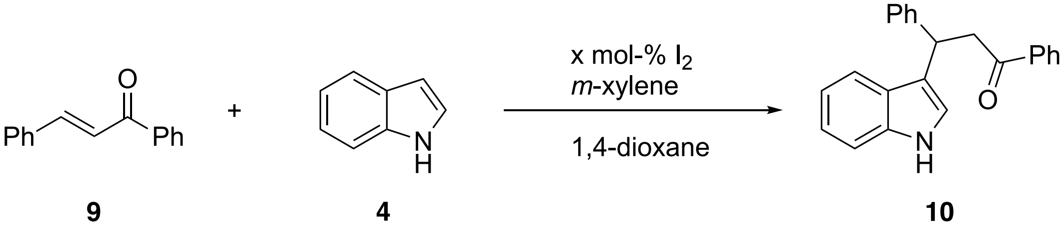
8.1 General Procedure

A temperature of 23 °C and an argon atmosphere was used for all kinetic runs. Measurements of kinetic data have been performed with a React-IR^{TM} 4000 delivered Mettler Toledo using ATR technique (Sensortype: SiComp). IR spectra have been collected every approx. 0.4 s and an average of 2 single spectra was determined. The reaction can either be followed by a prominent absorption band between 1700 and 1690 cm^{-1} or by using the automatic reaction analyzer implemented in the software iC IR 4.0 (Version 4.0.641.3) from Mettler Toledo. Both methods result in almost identical initial rates and the latter was chosen for the determination of the kinetics due to a better signal-to-noise ratio.

The initial-rate method was chosen to determine the reaction order in molecular iodine. To determine the initial rate, both the initial 10 % and the initial 15 % of product formation was considered. Both values result in very similar correlations with the employed concentrations of iodine (see below) with the initial rates after 10 % being slightly higher.

Besides correlating the initial rates with the iodine concentrations, we have also analyzed double-logarithmic plots [ln(initial rate) vs. ln [I_2])] for the same reactions. A slope of close to unity was observed (see below) in all cases.

8.2 Kinetics for the Iodine-Catalyzed Reaction of Indole (4) and *trans*-Chalcone (9) in 1,4-Dioxane



A solution of the staring materials and the internal standard (*m*-xylene) in 1,4-dioxane was stirred at 23 °C. A solution of molecular iodine was added and the kinetics were monitored by IR spectroscopy. In the course of the reaction, a new IR band appears at ca 1692 cm^{-1} (Figure S6). The product concentration at the end of the kinetic experiment was determined by ^{1}H NMR spectroscopy in d^6-

dimethylsulfoxide which also deactivates the reaction. Detailed reaction conditions and results are summarized in Table S15 and Figure S7. Correlation analyses are shown in Figure S8.

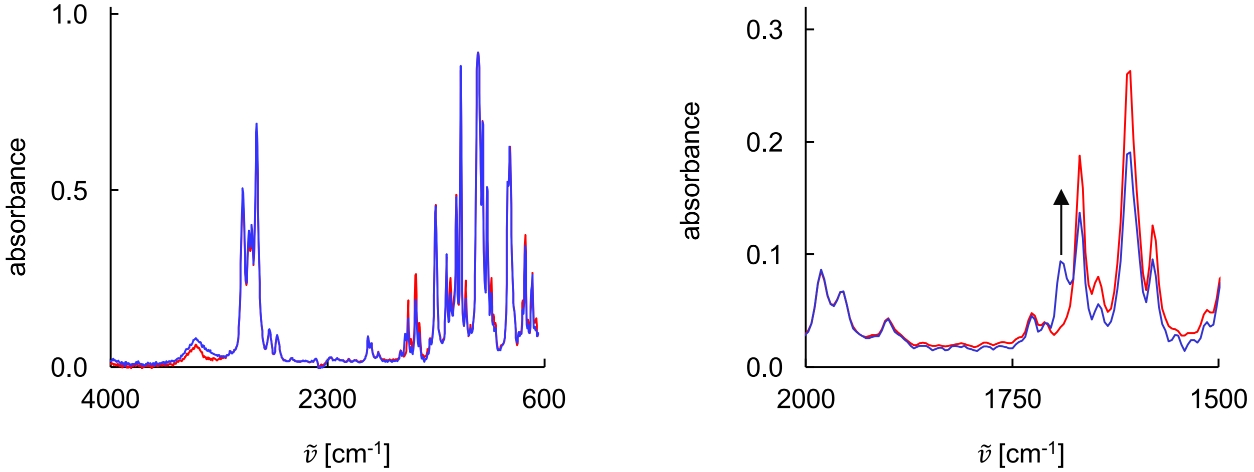


Figure S6: IR spectra immediately after mixing (in red) and after 25 minutes (in blue)for the iodine-catalyzed reaction between *trans*-Chalcone (**9**) and Indole (**4**) (1,4-Dioxane, 23 °C).

Table S15: Concentrations and Initial Rates (for 10 % and 15 % Conversion) for the Iodine-Catalyzed Reaction between *trans*-Chalcone (**9**) and Indole (**4**) (1,4-Dioxane, 23 °C).

4 [mol L^{-1}]	**9** [mol L^{-1}]	xylene [mol L^{-1}]	I_2 [mol L^{-1}]	mol-%	10 % initial rate [mmol L^{-1} s^{-1}]	15 % initial rate [mmol L^{-1} s^{-1}]
5.00×10^{-1}	5.00×10^{-1}	8.85×10^{-2}	2.46×10^{-3}	0.5	1.82	1.10
5.00×10^{-1}	5.00×10^{-1}	8.85×10^{-2}	4.93×10^{-3}	1.0	3.17	2.27
5.00×10^{-1}	5.00×10^{-1}	8.85×10^{-2}	7.39×10^{-3}	1.5	7.00	4.31
5.00×10^{-1}	5.00×10^{-1}	8.85×10^{-2}	9.85×10^{-3}	2.0	7.23	5.59

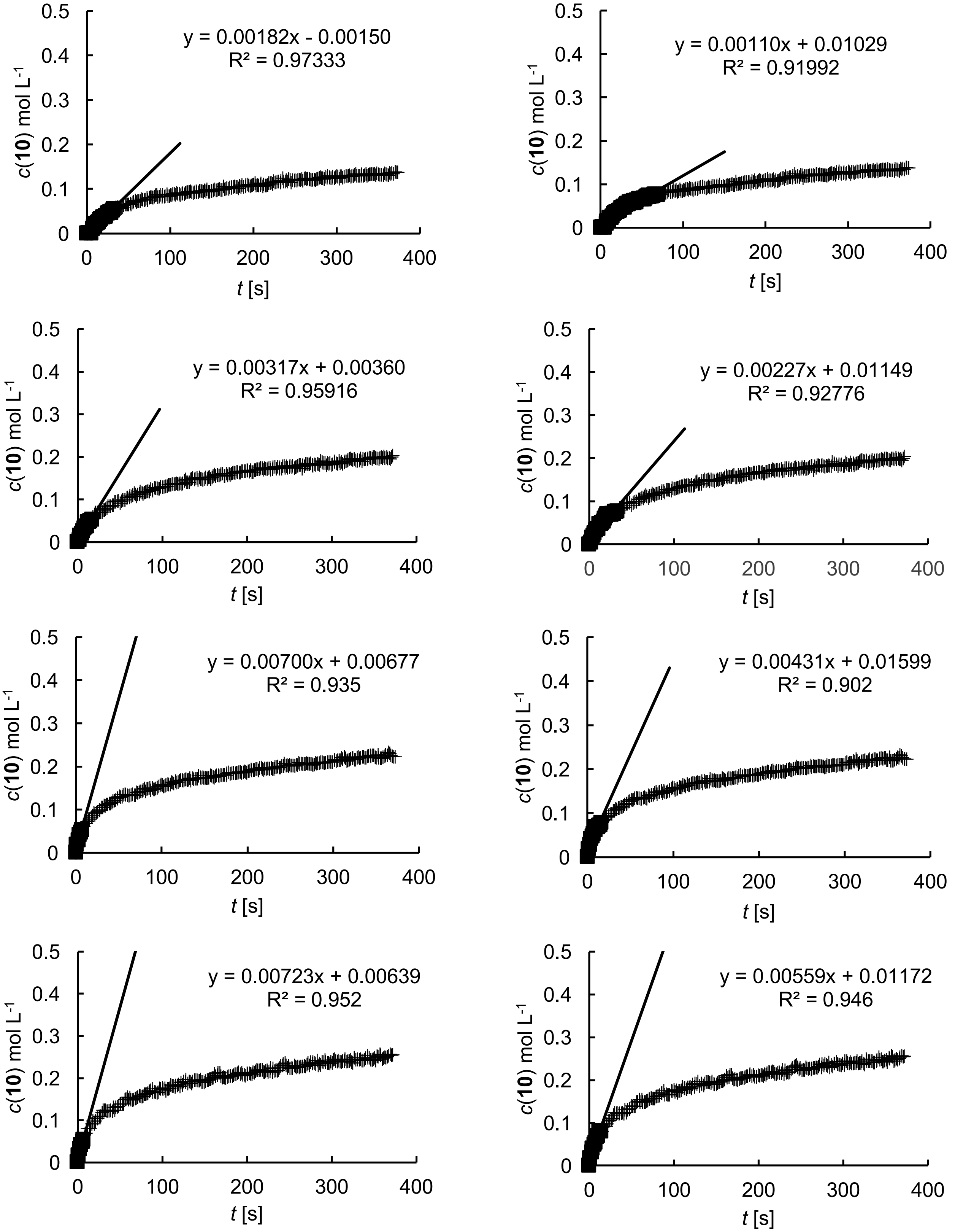


Figure S7: Concentration-time profiles used for the determination of initial rates (left: 10 % conversion, right: 15 % conversion) for the iodine-catalyzed reaction of **4** an **9** (23 °C, 1,4-dioxane).

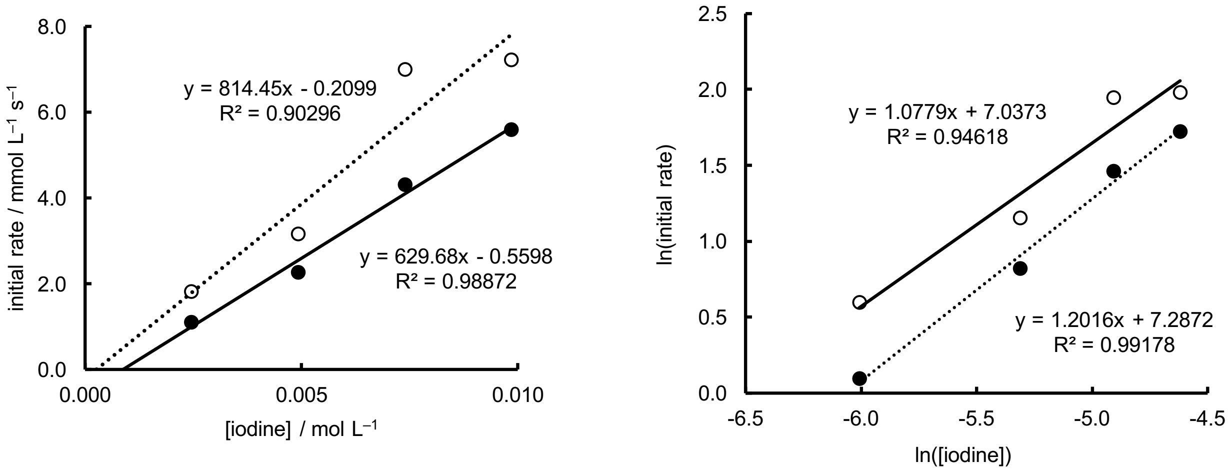


Figure S8: Correlation of initial rates vs. the iodine concentration (left) and double-logarithmic plots of the initial rates vs. the iodine concentrations (right) for the reaction between **9** and **4** (1,4-dioxane, 23 °C) considering up to 10% yield (filled dots) or up to 15% yield (open dots).

9 Kinetic Analysis using Reaction Calorimetry

9.1 General Procedure

Kinetic experiments were performed using an Omnical Multi-Reactor Calorimeter Insight_RT10. Reaction have been performed in a screw-cap-vial (10 mL) with a pierceable screw-cab under protective atmosphere. The vial was placed into a reactor port of the reaction calorimeter and all compounds except the catalyst were added. A syringe filled with a solution of iodine and a caped needle was placed into the syringe port. Reactions were generally conducted at 23 °C and thermal equilibrium was approximately attained after keeping the vials within the calorimeter for at least 25 minutes and the syringes for at least 15 minutes. The reactions were initiated by injecting the catalyst solution. The reaction progress could be controlled online. Agitation speed was 210 mot min^{-1}.

The yield at the end of the kinetic measurement was determined by taking a sample from the reaction mixture by syringe and quenching it by mixing with d^6-dimethylsulfoxide and the crude mixture was analyzed by ^{1}H NMR spectroscopy. Yields at the end of the reactions ($f_{yield}(t_{end})$) were determined from the ratio of standard to product peak integrals. Data points were usually taken every 6 seconds over the course of the reaction. The calorimetric experiments were performed and evaluated similar to known procedures and techniques published before.[S4]

The reaction heat flow q is proportional to the reaction rate r, where $\Delta H_{\mathrm{react}}$ is the heat of the reaction and V is the reaction volume (Eq. S4). This equation can be rearranged to give the initial reaction rate r when Δq and Δt in an early period of the reaction are considered (Eq. S5)

$$\frac{dq}{dt} = \Delta H_{react} \cdot V \cdot r \qquad \text{(S4)}$$

$$\frac{\mathrm{d}q}{\mathrm{d}t \cdot \Delta H_{react} \cdot V} = r \qquad \text{(S5)}$$

The observed heat flow profiles may also be used to obtain the fractional conversion f_{Yield} of limiting substrate by calculation of the fractional area under the temporal heat flow curve as given in equation (S6), where the numerator represents the area under the heat flow curve at any time point t and the denominator represents the total area under the heat flow curve after completion of the reaction at time t_{end}. The product yield at t_{end} was determined by ^{1}H NMR and was used to calculate the r_{max} value (rate at maximal heat flow).

$$fyield = fyield(t_{end}) \cdot \frac{\int_0^t q(t)dt}{\int_0^{t_{end}} q(t)dt} \qquad \text{(S6)}$$

9.2 Verification of the Kinetic Data by ^{1}H NMR Spectroscopy

A reaction vessel was charged with substrate, *p*-xylene and acetonitrile ([**9**] = 80 mM, [**11**] = 100 mM, [*p*-xylene] = 23 mM). An iodine solution was added to this mixture which started the reaction to result in 4.3 mol% iodine content. Figure S9 shows the fractional yield determined by the calorimetric method (black line) and the yield determined by ^{1}H-NMR samples of the reaction mixture which have been taken after approx. 3, 6 and 10 minutes as well as at the end of the measurement (15 minutes) (red dots).

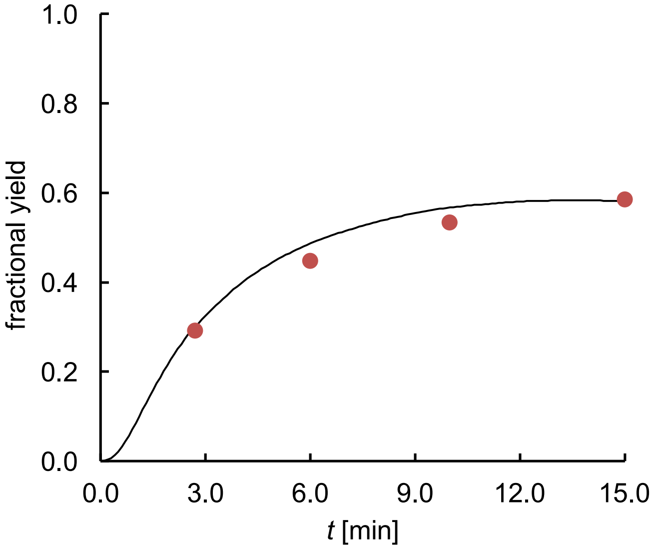
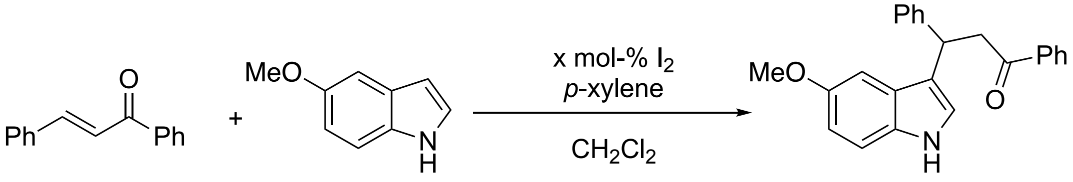


Figure S9: Fractional yield over time determined by heat flow (in black) and by 1H NMR spectroscopy (red dots) for the iodine-catalyzed reaction between **9** and **11** (4.3 mol% iodine, CH_3CN, 23 °C).

9.3 Kinetics for the Iodine-Catalyzed Reaction of 5-Methoxyindole (11) and *trans*-Chalcone (9) in Dichloromethane



9 **11** **12**

Substrate and standard were directly added to the reaction vessel and dissolved in dichloromethane. An iodine solution was added to this mixture which started the reaction. Detailed reaction conditions and results are summarized in Table S16 and Figure S10. Initial rates have been determined based on the maximal measured heat flow. Figure S11 shows the correlation between these initial rates and the employed iodine concentrations. The double logarithmic plot (Figure S11) also results in a reaction order of iodine close to unity.

Table S16: Concentrations and Rates at Maximal Heat Flow (r_{max}) for the Iodine-Catalyzed Reaction between *trans*-Chalcone (**9**) and 5-Methoxyindole (**11**) (CH_2Cl_2, 23 °C).

9 [mol L^{-1}]	**11** [mol L^{-1}]	xylene [mol L^{-1}]	I_2 [mol L^{-1}]	I_2 [mol%]	r_{max} [mmol L^{-1} s^{-1}]
2.00×10^{-1}	1.99×10^{-1}	6.19×10^{-2}	3.49×10^{-3}	1.8	8.05×10^{-3}
2.01×10^{-1}	2.01×10^{-1}	7.85×10^{-2}	1.05×10^{-2}	5.2	2.19×10^{-2}
2.02×10^{-1}	2.00×10^{-1}	5.78×10^{-2}	1.40×10^{-2}	7.0	2.72×10^{-2}

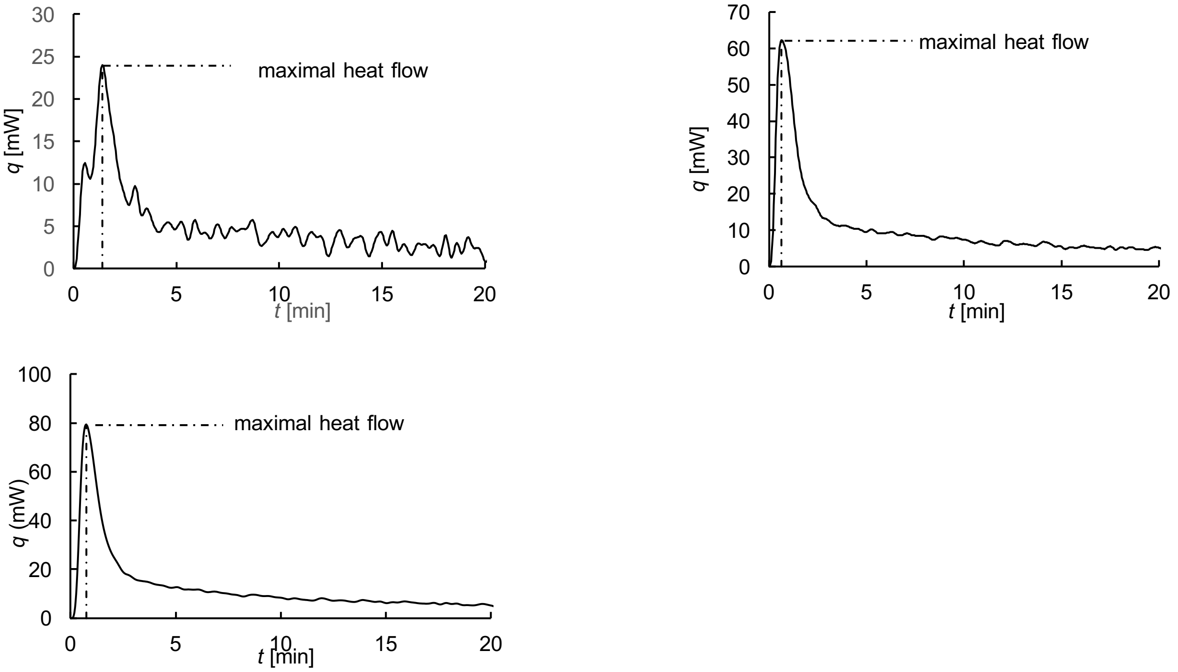


Figure S10: Heat flow profile of the reaction of **9** and **11** in the presence of 1.8 mol% (top left), 5.2 mol% (top right) and 7.0 mol% (bottom left) iodine (CH_2Cl_2, 23 °C).

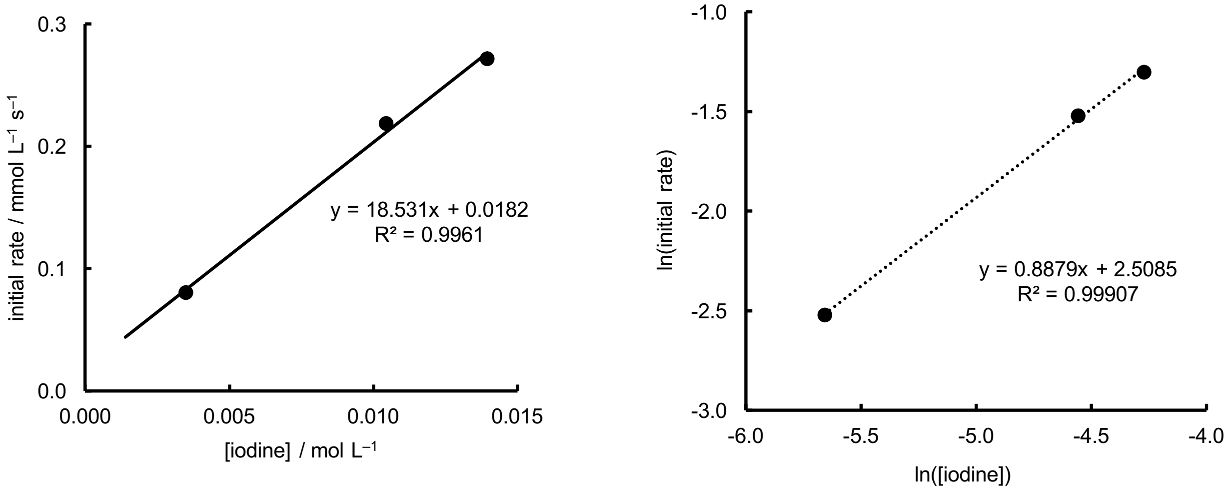
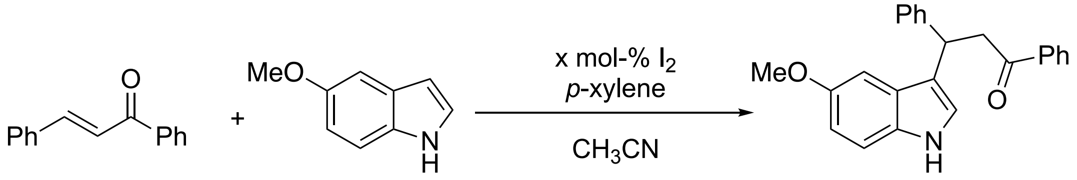


Figure S11: Correlation of initial rates vs. the iodine concentration (left) and double-logarithmic plots of the initial rates vs. the iodine concentrations (right) for the reaction between **9** and **11** (CH_2Cl_2, 23 °C).

9.4 Kinetics for the Iodine-Catalyzed Reaction of 5-Methoxyindole (11) and *trans*-Chalcone (9) in Acetonitrile



9 **11** **12**

Substrate and standard were directly added to the reaction vessel and dissolved in acetonitrile. An iodine solution was added to this mixture which started the reaction. Detailed reaction conditions and results are summarized in Table S17 and Figure S12. Initial rates have been determined based on the maximal measured heat flow. Figure S13 shows the correlation between these initial rates and the employed iodine concentrations. The double logarithmic plot (Figure S13) also results in a reaction order of iodine close to unity.

Table S17: Concentrations and Rates at Maximal Heat Flow (r_{max}) for the Iodine-Catalyzed Reaction between *trans*-Chalcone (**9**) and 5-Methoxyindole (**11**) (CH_3CN, 23 °C).

9 [mol L^{-1}]	**11** [mol L^{-1}]	xylene [mol L^{-1}]	I_2 [mol L^{-1}]	I_2 mol%	initial rate [mmol L^{-1} s^{-1}]
1.00×10^{-1}	8.00×10^{-2}	2.28×10^{-2}	1.73×10^{-3}	2.2	1.02×10^{-1}
1.00×10^{-1}	8.00×10^{-2}	2.28×10^{-2}	3.46×10^{-3}	4.3	1.94×10^{-1}
1.00×10^{-1}	8.00×10^{-2}	2.28×10^{-2}	5.19×10^{-3}	6.5	2.50×10^{-1}

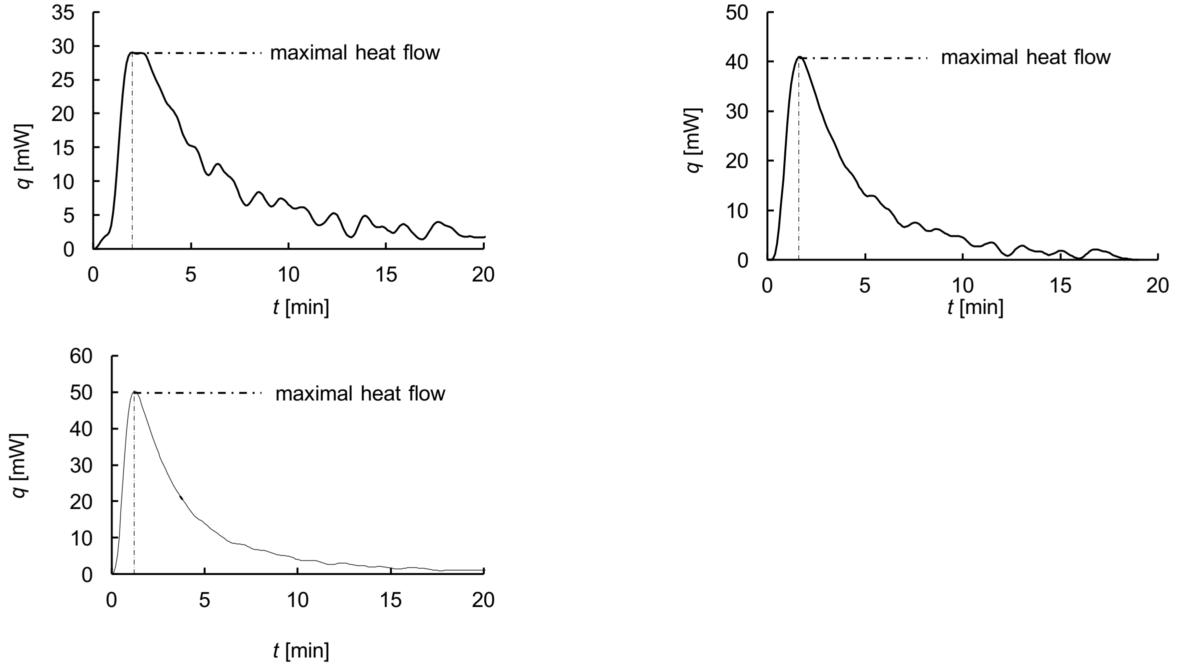


Figure S12: Heat flow profile of the reaction of **9** and **11** in the presence of 2.2 mol% (top left), 4.3 mol% (top right) and 6.4 mol% (bottom left) iodine (CH_3CN, 23 °C).

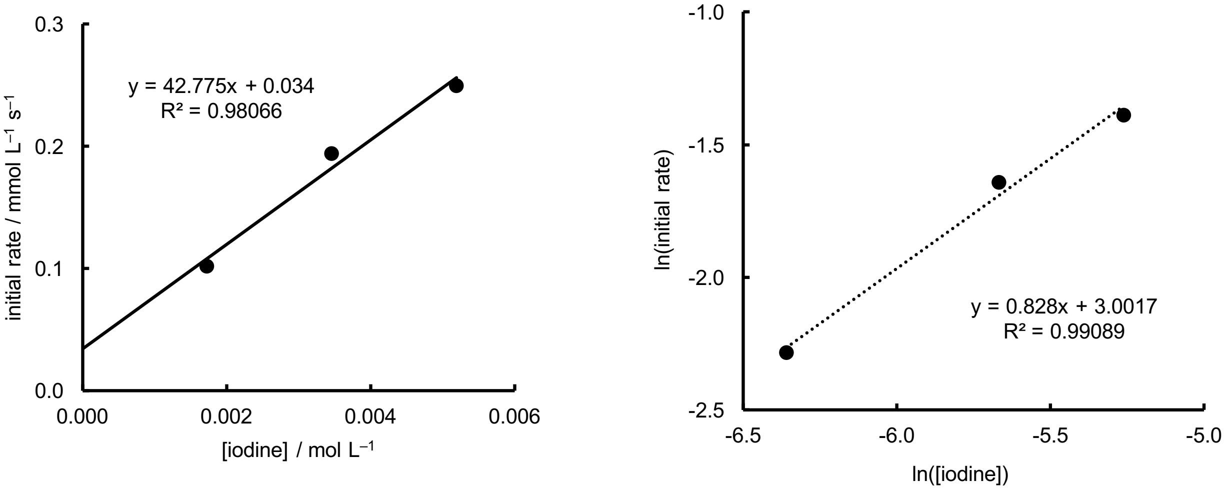
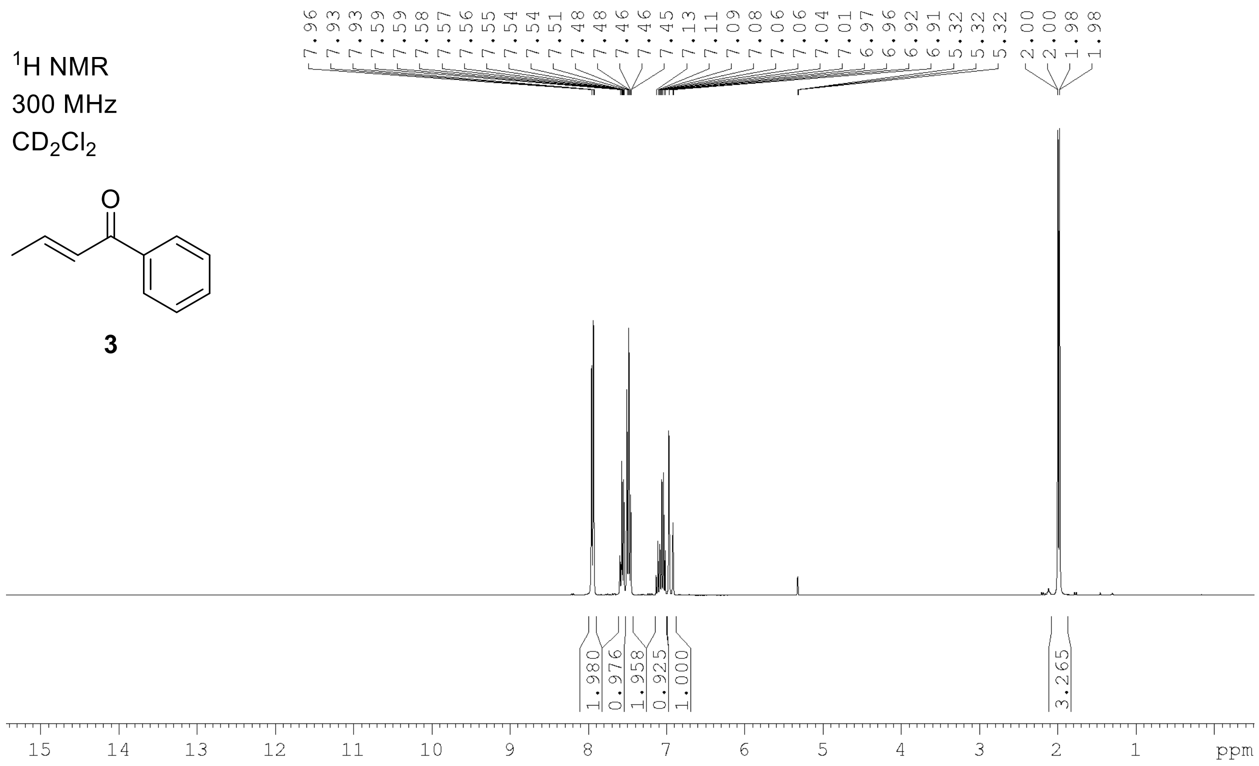
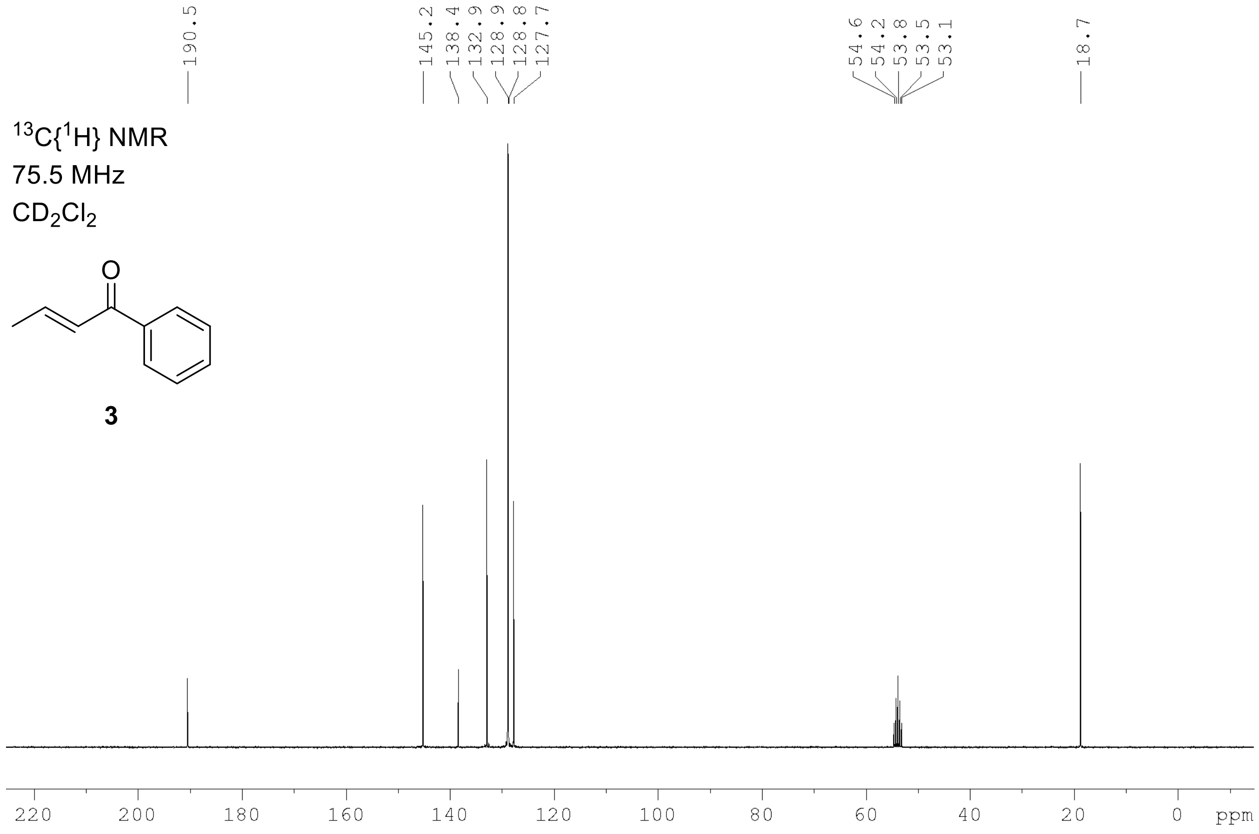


Figure S13: Correlation of initial rates vs. the iodine concentration (left) and double-logarithmic plots of the initial rates vs. the iodine concentrations (right) for the reaction between **9** and **11** (CH_3CN, 23 °C).

10 Copies of NMR Spectra





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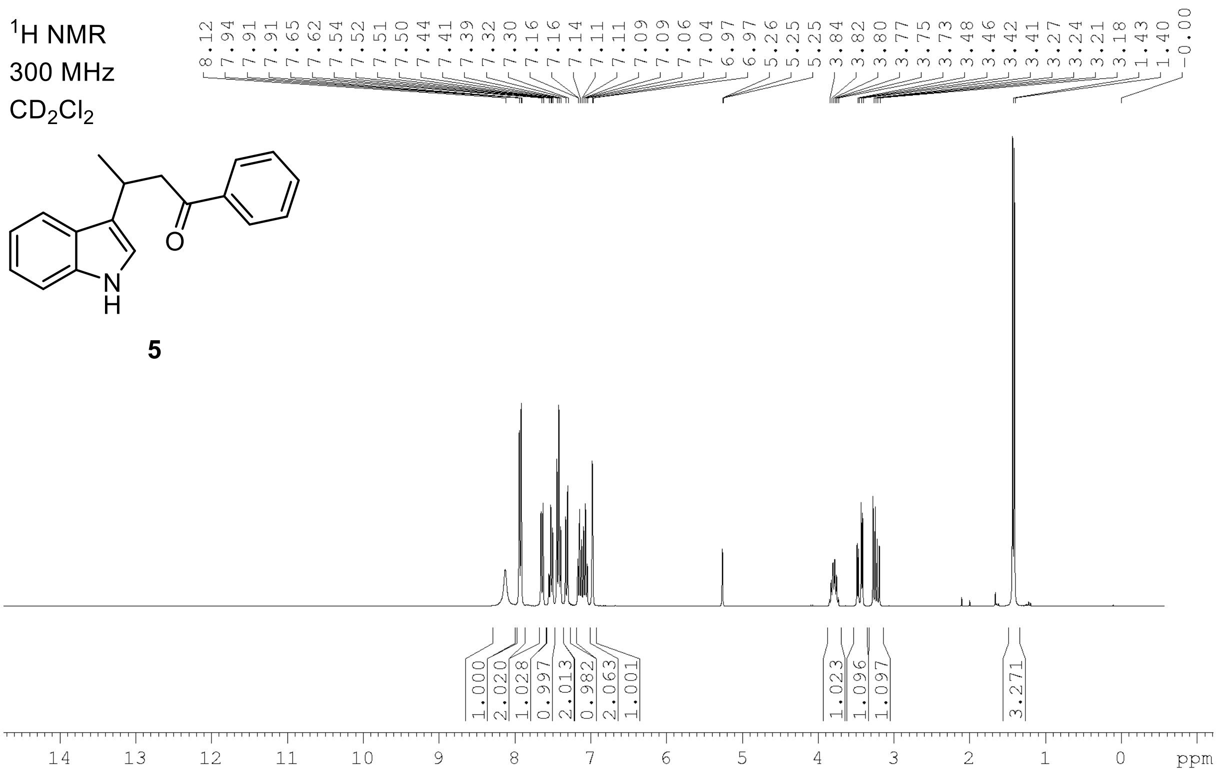
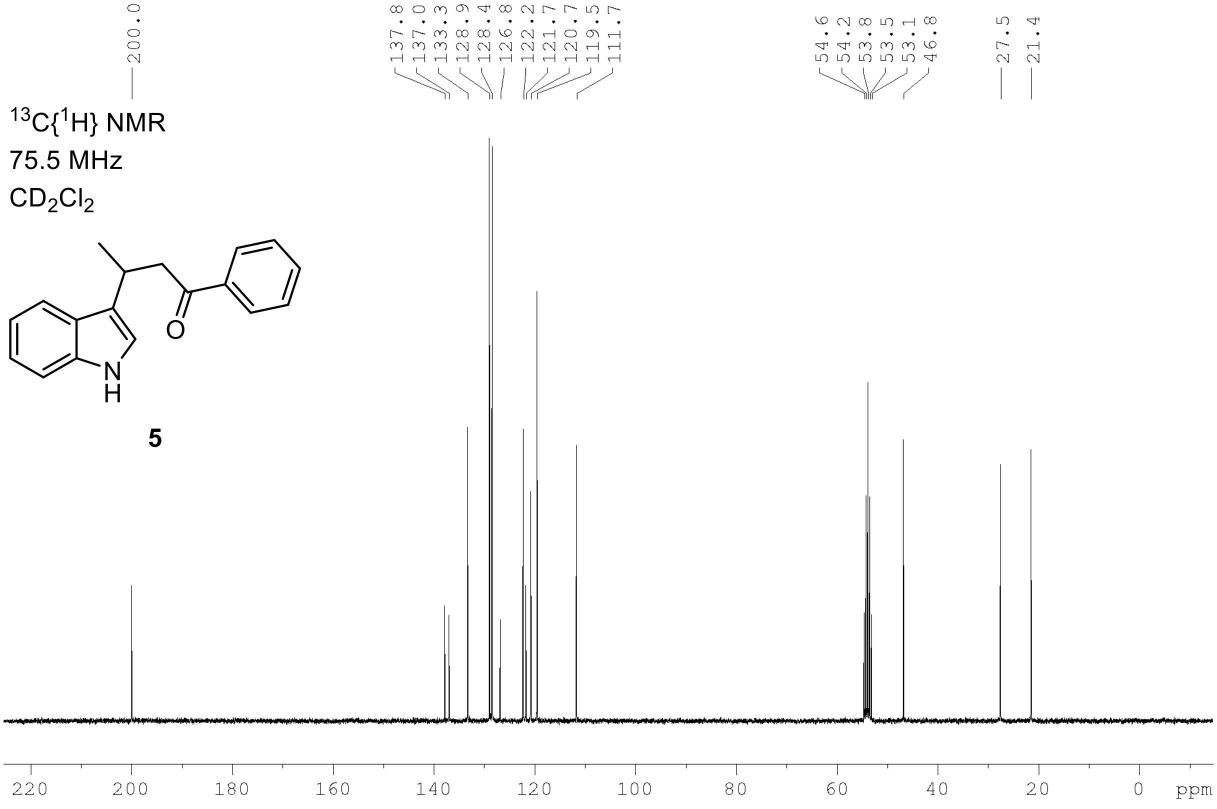
CD_2Cl_2



5

$^{13}C\{^1H\}$ NMR
75.5 MHz
CD_2Cl_2



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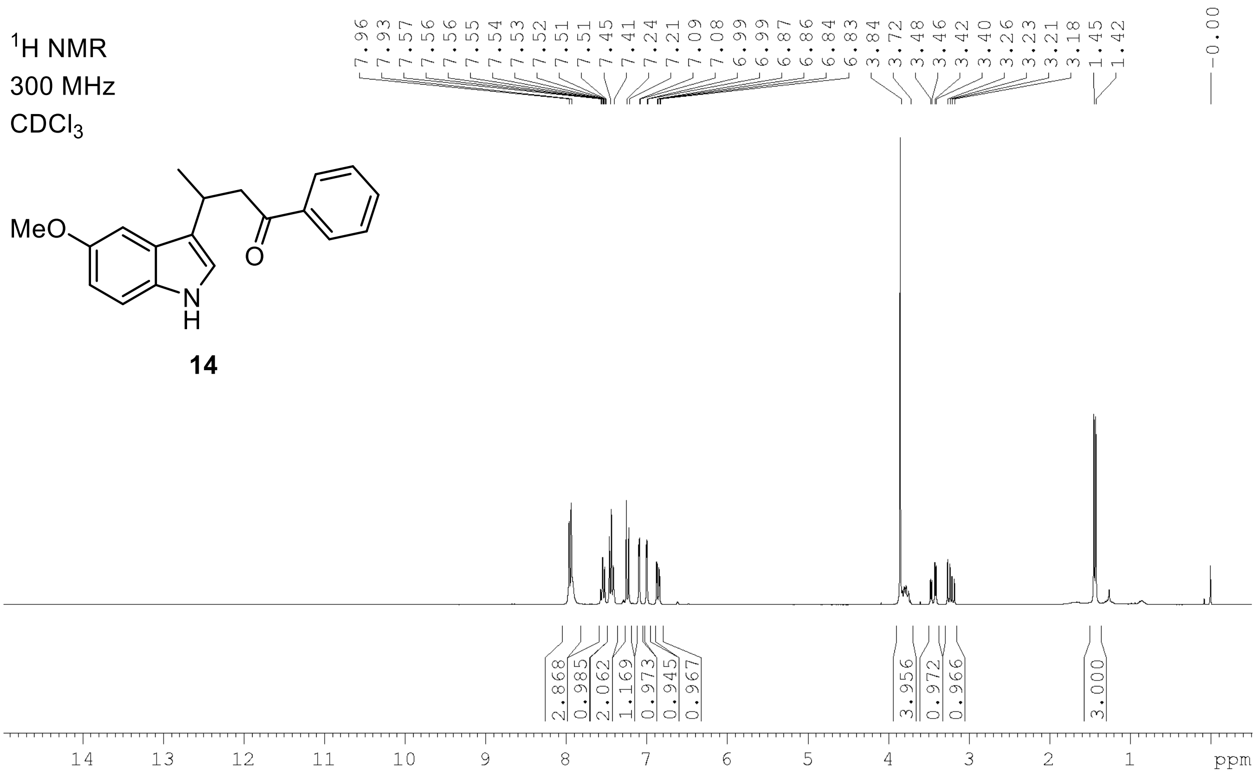
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N
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7.54
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7.51
7.51
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7.08
6.99
6.87
6.86
6.84
6.83
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3.72
3.48
3.46
3.42
3.40
3.26
3.23
3.21
3.18
1.45
1.42
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0.985
2.062
1.169
0.973
0.945
0.967
3.956
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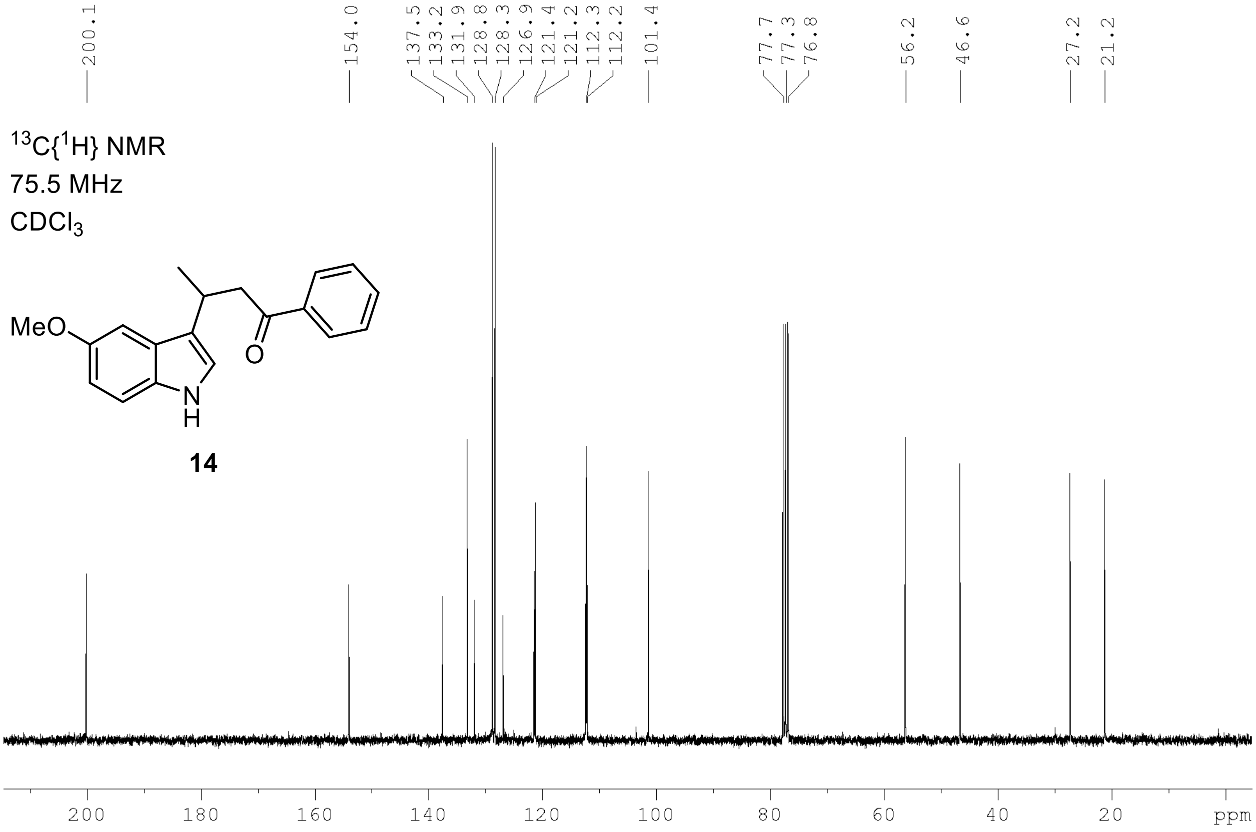
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77.7
77.3
76.8
56.2
46.6
27.2
21.2
$^{13}C\{^1H\}$ NMR
75.5 MHz
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MeO
O
N
H
14
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140
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100
80
60
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20
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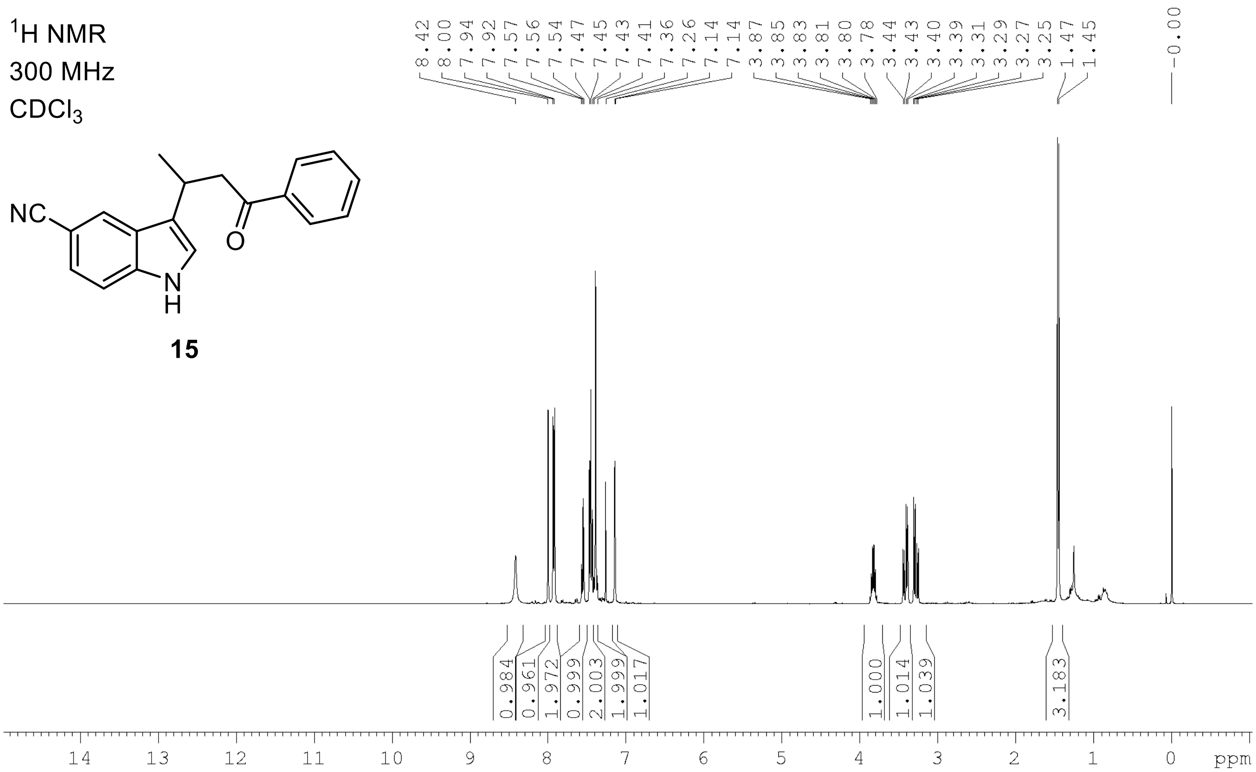
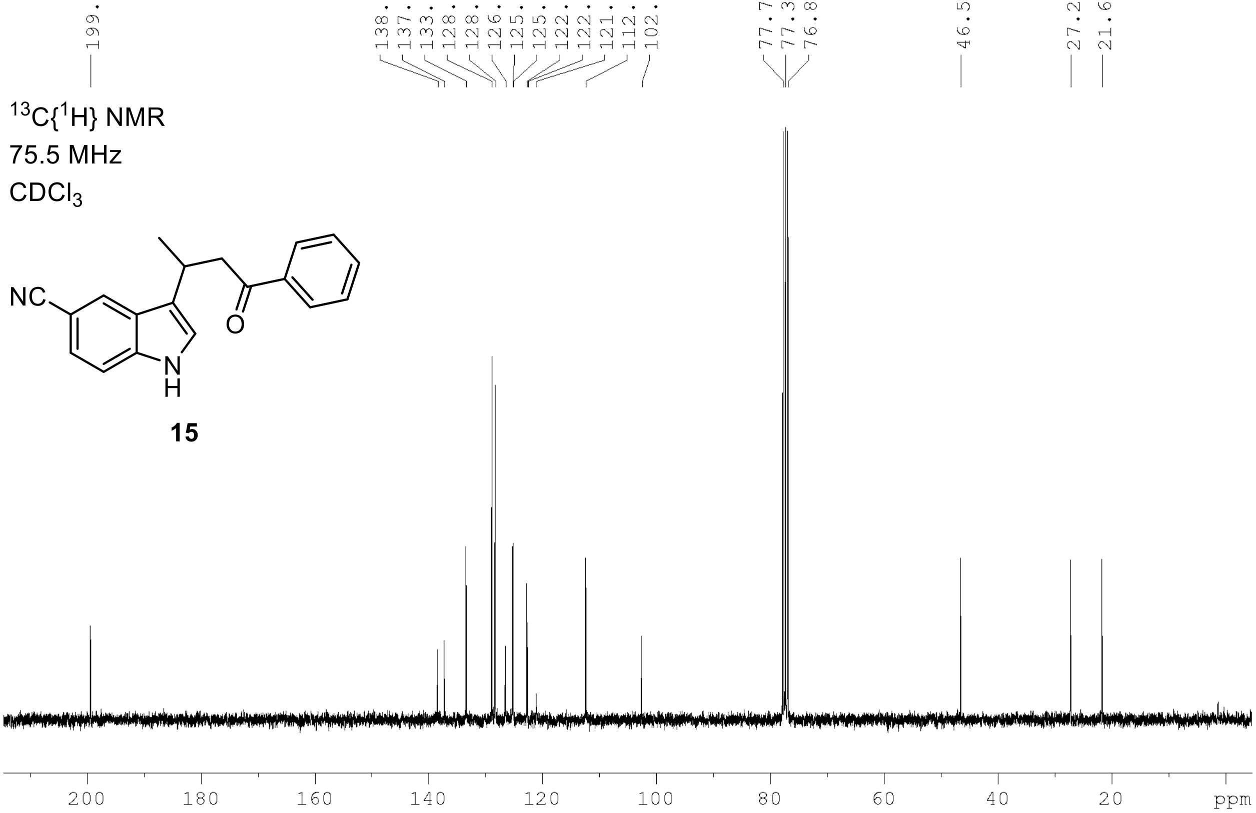


^1H NMR
300 MHz
$CDCl_3$

15



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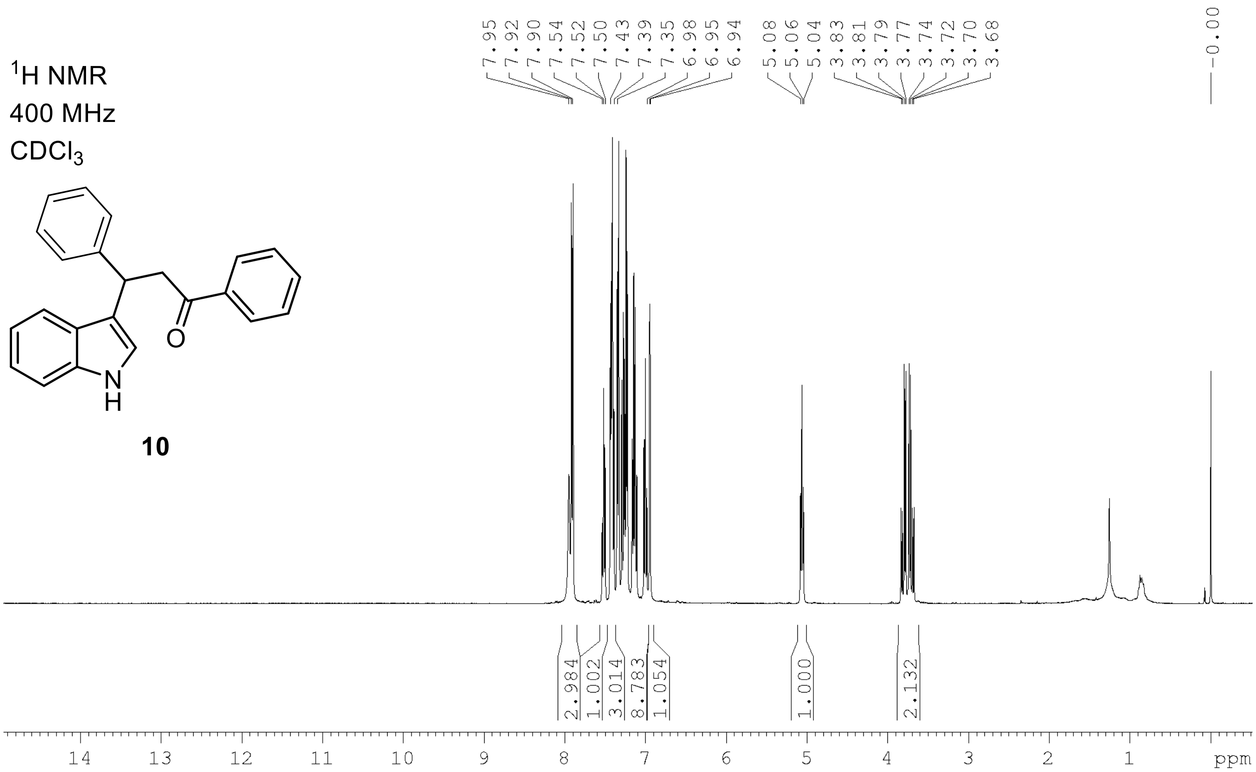
15



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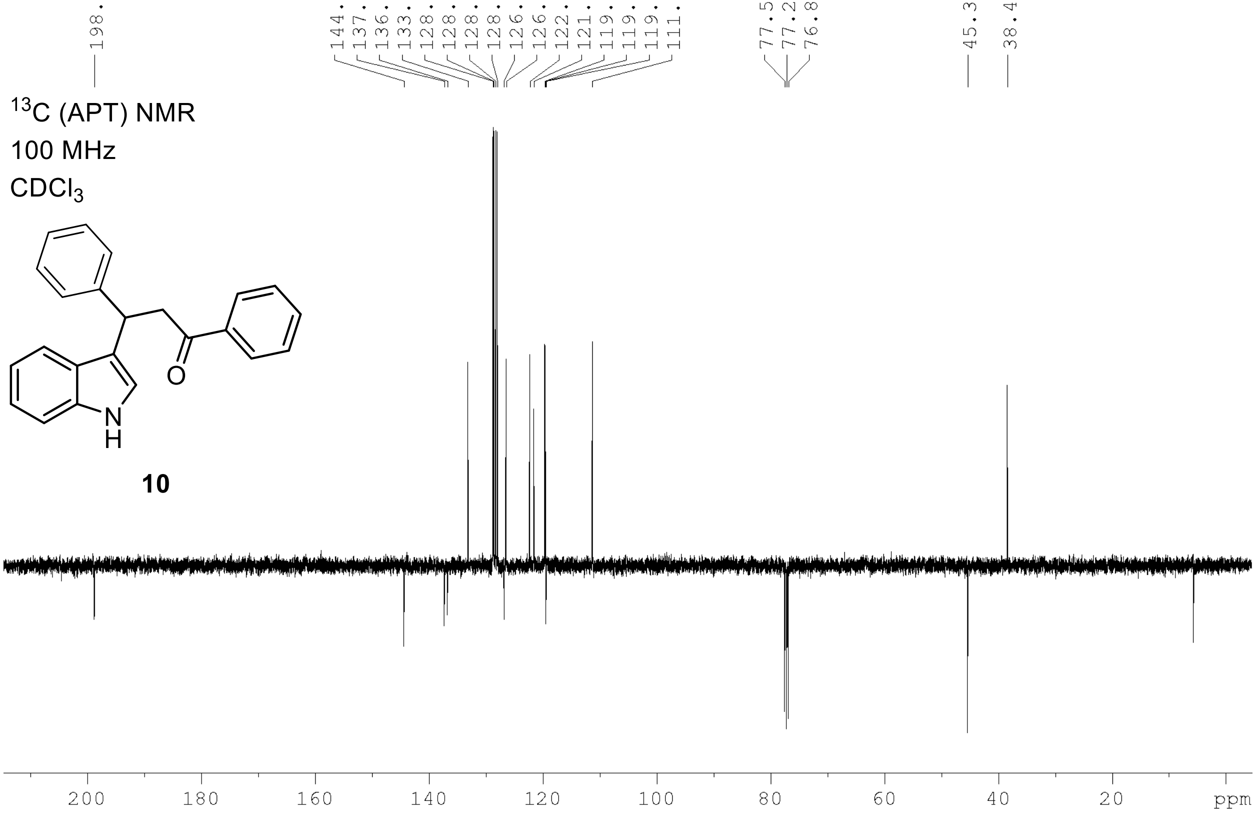

^{13}C (APT) NMR
100 MHz
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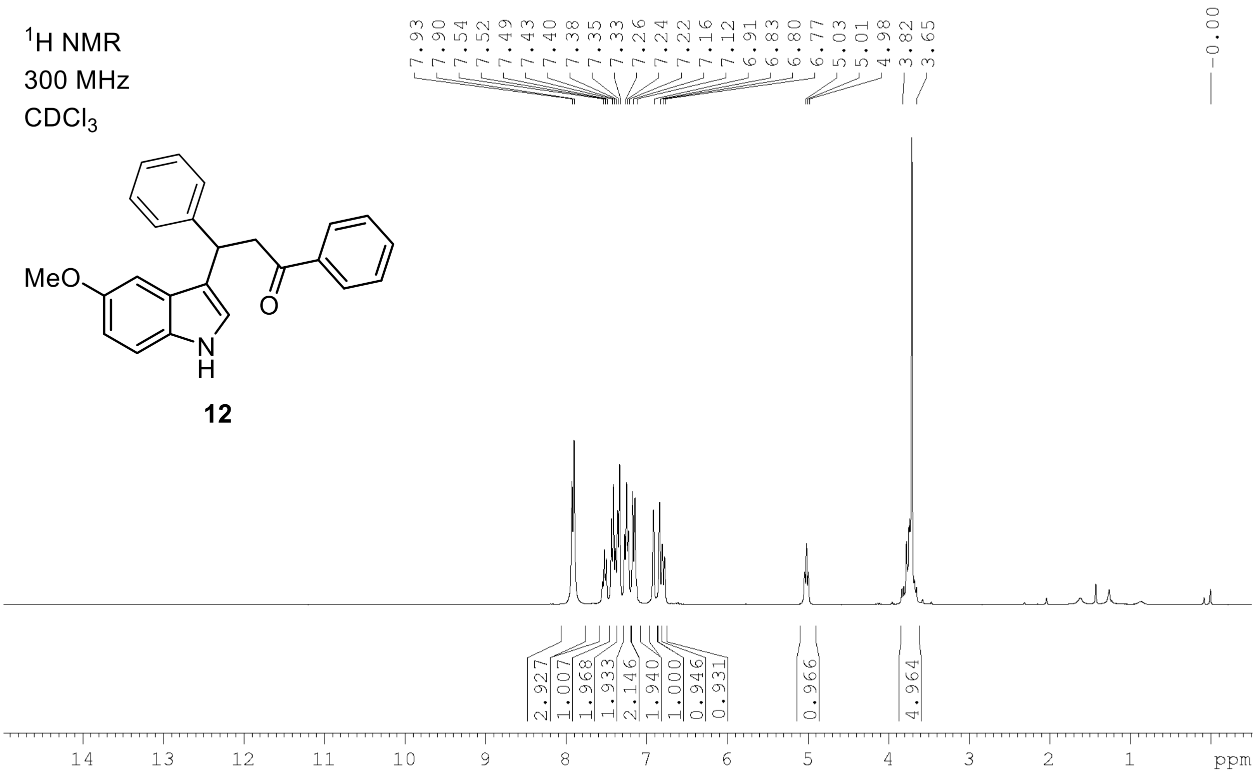
10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300 MHz
$CDCl_3$
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7.90
7.54
7.52
7.49
7.43
7.40
7.38
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7.33
7.26
7.24
7.22
7.16
7.12
6.91
6.83
6.80
6.77
5.03
5.01
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3.82
3.65
-0.00
MeO
O
N
H
2.927
1.007
1.968
1.933
2.146
1.940
1.000
0.946
0.931
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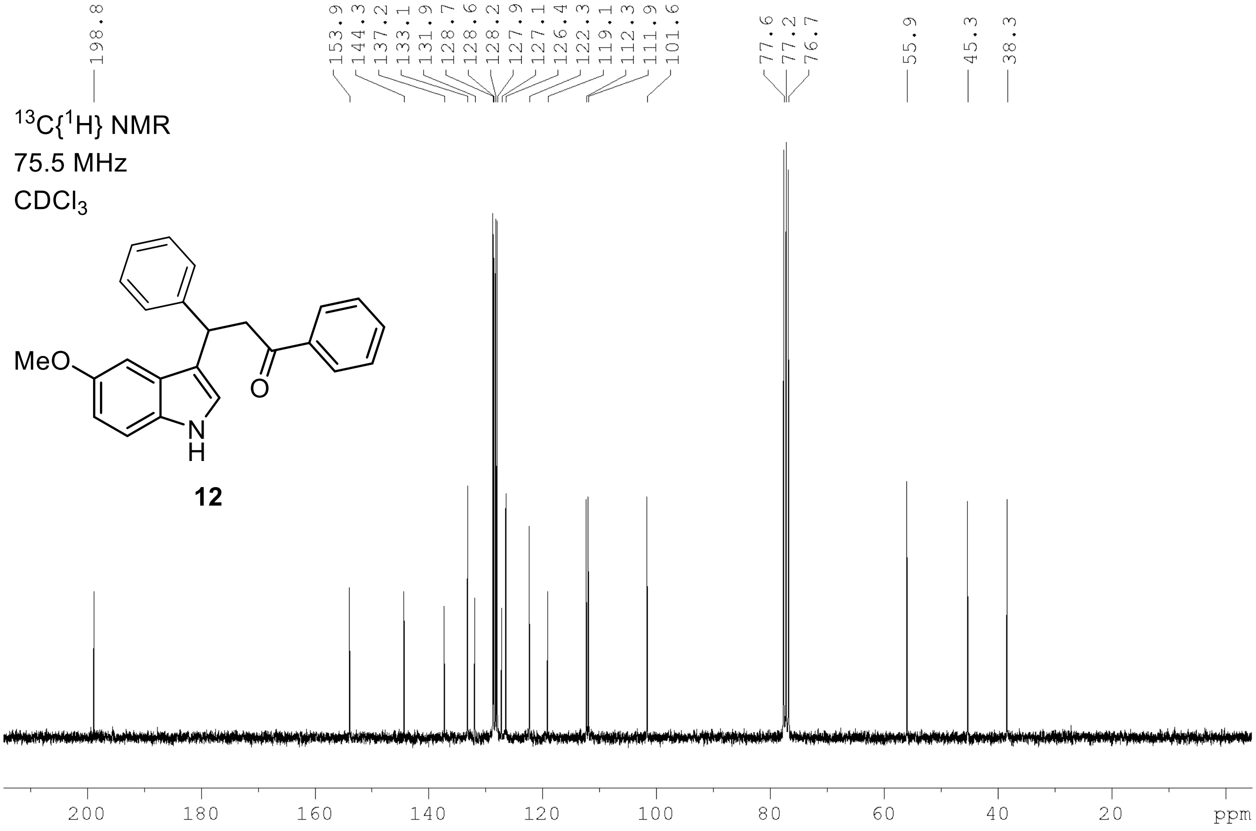
ppm

12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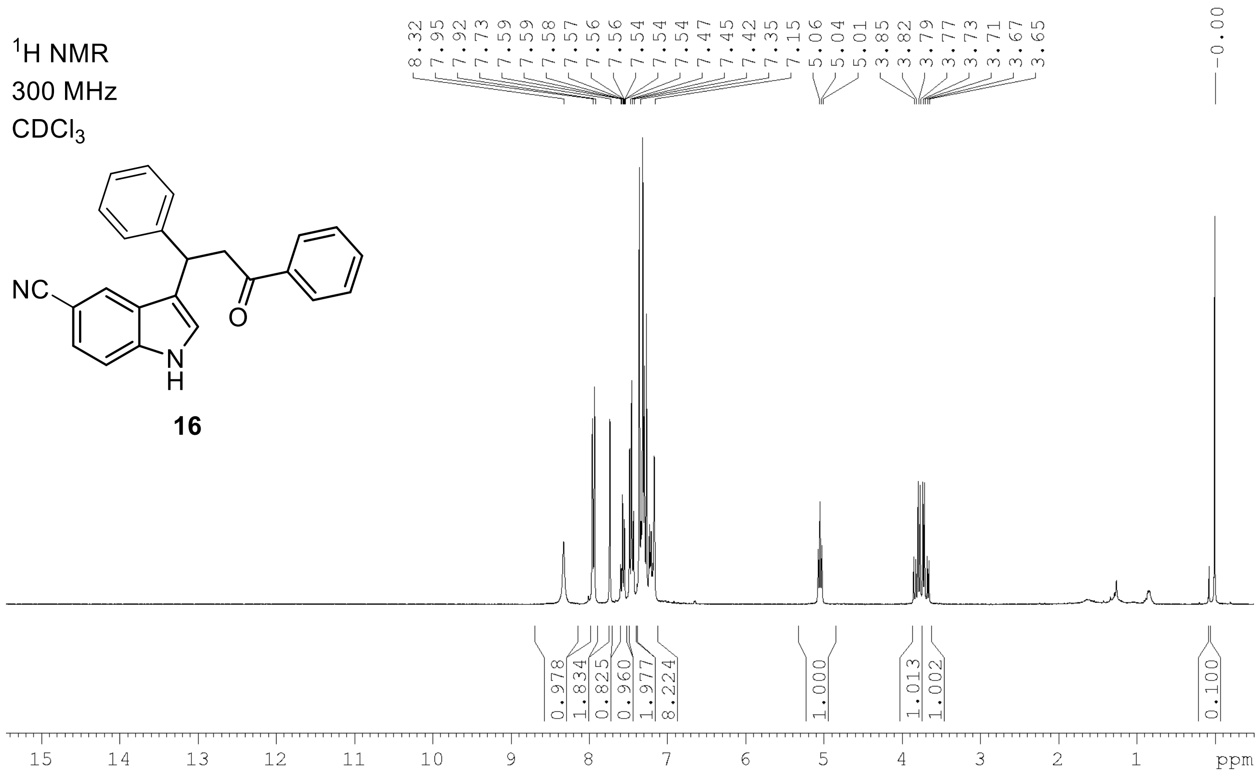
112.3
111.9
101.6
77.6
77.2
76.7
55.9
45.3
38.3
^{13}C{^{1}H} NMR
75.5 MHz
$CDCl_3$
MeO
O
N
H
200
180
160
140
120
100
80
60
40
20
ppm

12



^{1}H NMR
300 MHz
CDCl$_3$
NC
O
N
H
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7.95
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3.79
3.77
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3.65
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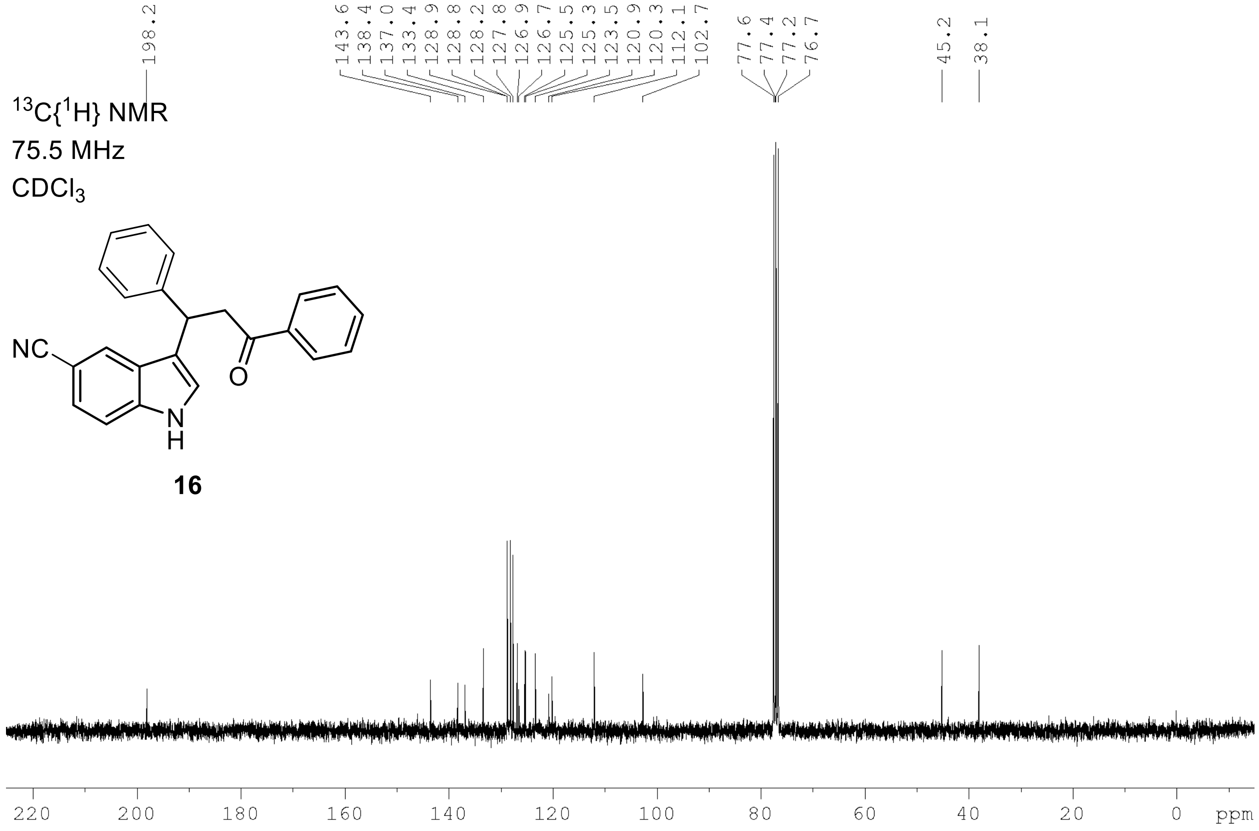
1.977
8.224
1.000
1.013
1.002
0.100
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

16



^{13}C{^{1}H} NMR
75.5 MHz
CDCl$_3$
NC
O
N
H
198.2
143.6
138.4
137.0
133.4
128.9
128.8
128.2
127.8
126.9
126.7
125.5
125.3
123.5
120.9
120.3
112.1
102.7
77.6
77.4
77.2
76.7
45.2
38.1
220
200
180
160
140
120
100
80
60
40
20
0
ppm

16

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