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Supporting Information

Dynamic Ureas with Fast and pH-Independent Hydrolytic Kinetics

Kaimin Cai,[a] Hanze Ying,[a] and Jianjun Cheng*[a, b, c, d, e, f, g]

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1. General procedures:

Materials. Chemicals were purchased and used as received unless otherwise specified. Anhydrous dimethylformamide (DMF) was dried with a column packed with 4Å molecular sieves. Tetrahydrofuran (THF) were dried with a column packed with alumina. Phosphate buffered saline (PBS) was purchased from Mediatech, Inc. HPLC grade 0.1% TFA-H_2O and acetonitrile were purchased from Fisher Scientific Company LLC (Hanover Park, IL, USA). All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Instrumentation. NMR spectra were recorded on a Varian U500 (500 MHz) or VXR-500 (500 MHz) spectrometer. All chemical shifts were reported in part per million (ppm). Tandem gel permeation chromatography (GPC) was performed on a system equipped with an isocratic pump (Model 1200, Agilent Technologies, Santa Clara, CA, USA), a DAWN HELEOS multi-angle laser light scattering detector (MALLS); (Wyatt Technology, Santa Barbara, CA, USA), and an Optilab rEX refractive index detector (Wyatt Technology). The detection wavelength of the HELEOS was set at 658 nm. Separations were performed on serially connected size exclusion columns (100 Å, 1000 Å, 10^4 Å, 10^5Å and 10^6 Å Phenogel columns, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA, USA) at 60 °C with DMF containing 0.1 M LiBr as the mobile phase. The HELEOS detector was calibrated with pure toluene without using external polymer standards and was used for the determination of the absolute molecular weights. The molecular weight of polymer was determined from the d_n/d_c value calculated assuming 100% mass recovery, and was processed by ASTRA software (Version 6.1.1, Wyatt Technology). THF GPC was equipped with one column (1000 Å, Phenogel columns, 5 μm, 300 × 7.8 mm, Phenomenex, Torrance, CA, USA) at room temperature and an Optilab rEX refractive index detector (Wyatt Technology). Poly(styrene) standards were used to get a calibration curve of M_w-elution time. The relative Mw of poly ureas were obtained from the calibration curve. HPLC analysis was conducted by Shimadzu LC system (LC-20AT) connected with PDA detector (SPD-M20A). Phenomenex Kinetex Ph-hexyl column (5 μm, 100 mm × 4.6 mm) was used for analysis. Gradient method was adopted using 0.1 % TFA-H_2O and acetonitrile as mobile phase. LC-MS was conducted by Waters Synapt G2Si instrument using Waters Cortecs UPLC C18 column (1.6 μm, 50 mm × 2.1 mm).

Synthesis of *N*-*t*-butyl-*N*-ethyl-*N'*-aryl urea.

Aryl isocyanate (0.20 mmol) was mixed with *N*-*t*-butyl- ethylamine (26 mg, 36 μL, 0.26 mmol) in methylene chloride (0.5 mL). The precipitates (hydrolyzed urea/aryl amine from the isocyanate if present) were discarded through centrifugation. Then solvent was removed completely under vacuum giving white (4-methoxyphenyl and phenyl tBEU)/ yellow (4-nitrophenyl tBEU) powder as pure product as confirmed by ^{1}H NMR.

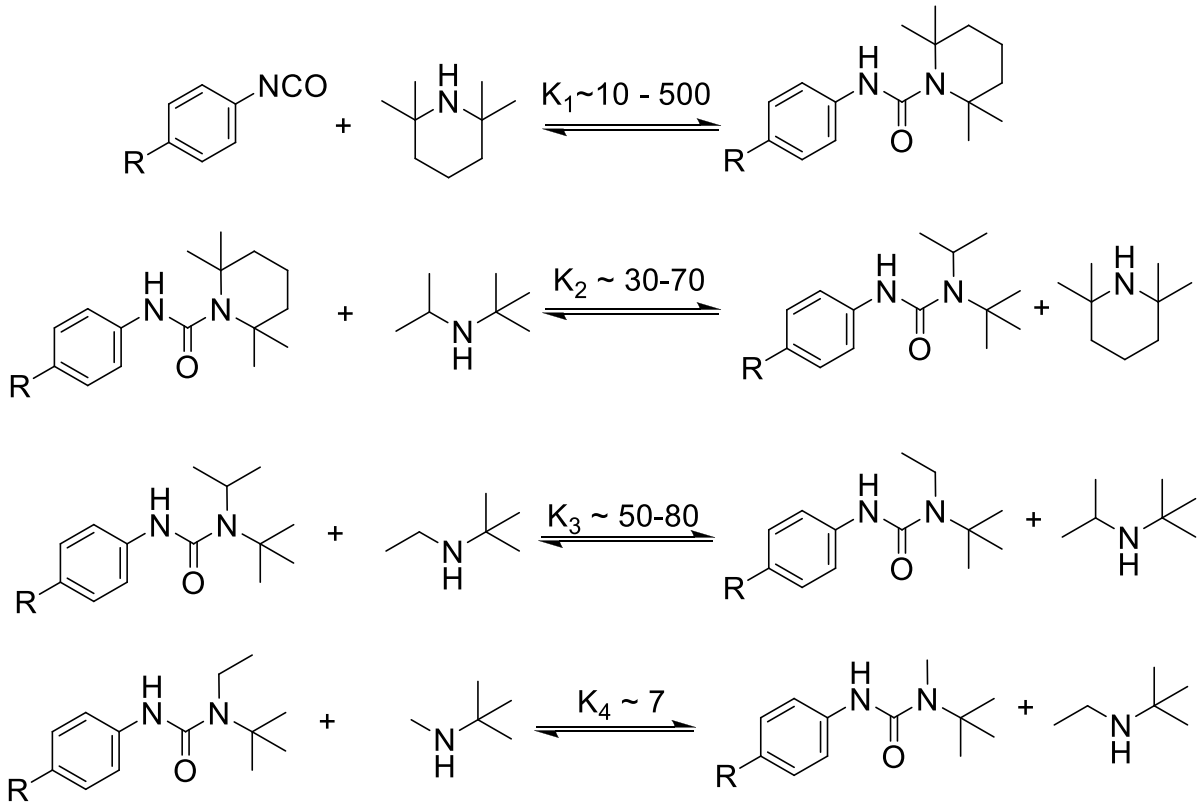
MeO-Ph-tBEU: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.23 (d, 2H, J = 9.0 Hz), 6.83 (d, 2H, J = 9.0 Hz), 6.18 (br, 1H), 3.77 (s, 3H), 3.38 (q, 2H, J = 7.5Hz), 1.47 (s, 9H), 1.28 (t, 3H, J = 7.5Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 155.7, 132.6, 122.5, 114.2, 56.5, 55.7, 39.6, 29.6, 17.0. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{23}N_2O_2^+$, 251.1754; observed, 251.1759.
Ph-tBEU: ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.33 (dd, 2H, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.27 (dd, 2H, J_1 = 7.0 Hz, J_2 = 8.5 Hz), 7.00 (dt, 1H, J_1 = 7.0 Hz, J_2 = 1.5 Hz), 6.31 (br, 1H), 3.77 (s, 3H), 3.39 (q, 2H, J = 7.0Hz), 1.48 (s, 9H), 1.29 (t, 3H, J = 7.0Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 139.6, 128.9, 122.8, 120.1, 56.6, 39.7, 29.6, 17.0. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{21}N_2O^+$, 221.1648; observed, 221.1648.

NO_2-Ph-tBEU: ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.15 (d, 2H, J = 9.0 Hz), 7.50 (d, 2H, J = 9.0 Hz), 6.68 (br, 1H), 3.42 (q, 2H, J = 7.0Hz), 1.49 (s, 9H), 1.30 (t, 3H, J = 7.0Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 146.1, 142.2, 125.1, 118.6, 57.2, 39.7, 29.4, 17.0. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{20}N_3O_3^+$, 266.1499; observed, 266.1514.

Equilibrium constant measurement for aryl hindered urea in *d*-chloroform.
The equilibrium constant (K_{eq}) was measured through indirect method used previously.[1] The K_{eq} of the hindered urea bond increases with the decrease of the substituents bulkiness. Briefly, the K_{eq} of the equilibrium shown in Scheme S1 was measured in *d*-chloroform and the K_{eq} of each aryl urea was calculated accordingly (Figure S1-S12). The results were summarized in Table S1.

Scheme S1. Chemical structure and binding constant measurement of bulky aryl ureas.



Determination of dissociation constant (k_{-1}) of aromatic hinder ureas.

***N*-*t*-butyl-*N*-ethyl-*N'*-aryl urea (tBEU)**

The dissociation constant (k_{-1}) of corresponding hinder ureas were determined through exchange experiment. Briefly, a *d*-chloroform(550 µL) solution of tBEU (0.050 mmol) was mixed with *N*-methyl-*t*-butyl-amine (1 eq). Then the mixture was monitored with ^{1}H NMR. The ratio of the two ureas was quantified by integration of the methyl/methylene hydrogen adjacent to the nitrogen atom. (Figure S13-S15) Linear regression of $\ln(\frac{[c_{\mathrm{tBEU}}]}{[c_{\mathrm{tBEU}}]_0} - \mathrm{A}) \sim t$ giving the slope as the dissociation constant (k_{-1}), in which A = $[c_{\mathrm{tBEU}}]/([c_{\mathrm{tBEU}}]+[c_{\mathrm{tBMU}}])$.[1a] (Figure S16)

***N*,*N*-diethyl-*N'*-aryl urea and *N*-*t*-ethyl-*N*-isopropyl-*N'*-aryl urea.**

Similar method as tBEU was adopted except that 10 equivalent *t*-butylamine or *n*-butyl amine was used. (Figure S17-S18) All of the obtained k_{-1} are summarized in Table S2.

Determination of hydrolysis kinetics of hindered aromatic urea bonds (HAU) in d_6-DMSO at 37 °C by ^{1}H NMR.

In a typical experiment, tBEU (5 mg) was dissolved in d_6-DMSO (475 µL) and H_2O (25 µL). The clear solution was then placed in NMR instrument at 37 °C. The composition was constantly monitored by ^{1}H NMR every 5 minutes. The urea percent was quantified by the peak integration ratio of the *t*-butyl group in the urea (9 H, 1.38-1.43 ppm) over *t*-butyl+methylene group in the amine (11 H, 0.99-1.06 ppm). (Figure S20-S22)

HPLC analysis of Ph-tBEU hydrolysis kinetics in 50:50 DMSO-H_2O at 37 °C.

Ph-tBEU stock solution was prepared in DMSO as 2 mg/mL. The solution was diluted with 1:1 DMSO/buffer to 20 µg/mL (~10^{-4} M) and incubated at 37 °C. At specified time, the solution was analyzed by HPLC to quantify the remaining tBEU content by HPLC standard calibration curve (λ_{abs} = 264 nm).

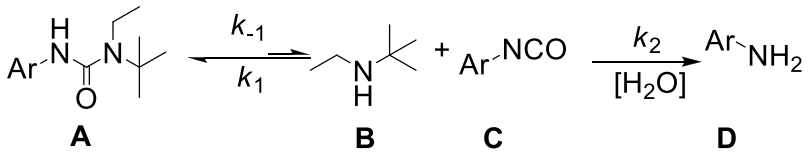
The standard sample of Ph-tBEU was prepared by diluting the above stock solution with acetonitrile to a 2 fold serial dilution and analyzed instantly after preparation. The pH 3-11 buffer cocktail was prepared by mixing 0.1 M Na_2HPO_4, $(NH_4)_2CO_3$, citric acid and adjusted pH using 1 M NaOH/HCl (aq), monitored by pH meter to 0.1 unit.

Determination of Ph-tBEU dissociation constant (k_{-1}) in 50:50 DMSO-H_2O at 37 °C.

To a 1:1 DMSO/H_2O solution of Ph-tBEU (1 mg/mL) was added *t*-butyl amine (5 µL, ~10 equiv). The clear solution was then incubated in 37 °C shaker. At specified time point, an aliquot of 20 µL was diluted with 980 µL 0.1 % TFA-H_2O for HPLC analysis. The Ph-tBEU concentration was quantified by standard calibration curve (λ_{abs} = 242 nm). Different from that of hydrolysis experiment, a new peak representing exchanged urea (*N*-*t*-butyl phenyl urea) showed up and its integrated UV absorption area matched the disappearance of the Ph-tBEU (Figure S23a)

indicating the reaction was exclusively amine exchange with negligible hydrolysis. The identity of Ph-tBEU and the generated *N*-t-butyl-*N*'-phenyl urea were confirmed by LC-MS (Figure S23c&d). The dissociation constant and half life of the tBEU was calculated through linear regression of ln([tBEU]/[tBEU]$_0$)-*t* (Figure S23b).

Kinetic analysis of dynamic urea hydrolysis



The hydrolysis of the urea can be expressed as:

$$r(hydrolysis) = -\frac{d[\boldsymbol{A}]}{dt} = \frac{d[\boldsymbol{D}]}{dt} = k_2[\boldsymbol{C}][H_2O] \quad (1)$$

Since the isocyanate **C** is an intermediate with very low concentration during hydrolysis, a steady-state approximation expressed as Equation (2) can thus be deduced:

$$k_2[\boldsymbol{C}][H_2O] + k_1[\boldsymbol{B}][\boldsymbol{C}] = k_{-1}[\boldsymbol{A}] \quad (2)$$

$$[\boldsymbol{C}] = \frac{k_{-1}[\boldsymbol{A}]}{k_1[\boldsymbol{B}] + k_2\,[H_2O]} \quad (3)$$

When $k_2[\boldsymbol{C}][H_2O] \gg k_1[\boldsymbol{B}][\boldsymbol{C}]$

The concentration of ***C*** can be simplified as following:

$$[\boldsymbol{C}] = \frac{k_{-1}[\boldsymbol{A}]}{k_1[\boldsymbol{B}] + k_2\,[H_2O]} \approx \frac{k_{-1}[\boldsymbol{A}]}{k_2\,[H_2O]} \quad (4)$$

The hydrolysis rate of the HAU is

$$r(hydrolysis) = -\frac{d[\boldsymbol{A}]}{dt} = k_2[H_2O][\boldsymbol{C}] = k_2[H_2O] \times \frac{k_{-1}[\boldsymbol{A}]}{k_2\,[H_2O]} = k_{-1}\,[\boldsymbol{A}] \quad (5)$$

Which is a first order kinetic with the HAU bond dissociation constant as the apparent hydrolysis rate k_{obs} as the urea dissociation is the rate-determining step during hydrolysis.

Synthesis of MDI- tBEU polymer and stability test under ambient condition.

4,4'-Methylene diphenyl diisocyanate (MDI) (100 mg, 0.40 mmol) was mixed with *N*,*N*'-di-*t*-butyl-ethylenediamine (69 mg, 86 µL, 0.40 mmol) in chloroform (300 µL) at room temperature for 5 minutes. Then solvent was removed under vacuum pump giving a white powder as polymer. The polymer powder was stored in a capped 7 ml scintillation vial without seal. The polymer was dissolved and analyzed in *d*-chloroform by ^{1}H NMR over 2 month. No peaks were observed in region δ 6.5-6.9 ppm indicating no hydrolytic aryl amine product in the polymer.

Determination of pHAU hydrolysis kinetics in water containing organic solvent.

The stored MDI-tBEU polymer powder was dissolved in THF as a 5 mg/mL solution and mixed with 5 % *v/v* buffer cocktail of pH 3, 7, and 11. The clear solution was then incubated at room temperature (25 ^{o}C) and the M_w was monitored by THF GPC at room temperature (one Phenomenex Phenogel 5 µm column, 10^3 Å).

Control polymer (MDI-DEU) preparation and degradation in 5% H_2O containing DMF at 37 ^{o}C[a].

MDI (1.05 g, 4.2 mmol) was mixed with *N, N'*-di-ethyl ethylene diamine (488 mg, 4.2 mmol) in chloroform (2 mL) at room temperature. White precipitates formed immediately and were sonicated for 20 minutes. Then the solvent was removed under vacuum and the polymer was obtained as white powder. The polymer was dissolved in DMF as 5 mg/ml solution and mixed with 5 % *v/v* H_2O. The clear solution was then incubated at 37 ^{o}C and the M_w was monitored by DMF GPC at 60 ^{o}C.

[a] The MDI-DEU was not well-dissolved in THF so DMF was used as solvent for the degradation study instead.

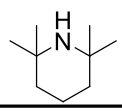
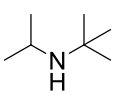
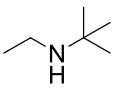
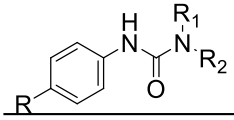
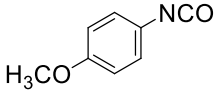
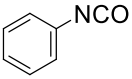
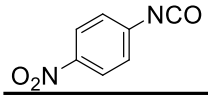
			
	tMPCA	tBIPU	tBEU	tBMU
	13	4.9×10^{2}	2.8×10^{4}	2.0×10^{5}
	16	5.4×10^{2}	3.0×10^{4}	2.1×10^{5}
	5.6×10^{2}	3.6×10^{4}	2.6×10^{6}	2.0×10^{7}

Table S1. Equilibrium constant of aromatic ureas with varying steric hindrance on amine. The equilibrium constant of tMPCA was calculated directly from ^{1}H NMR (Figure S1, S5 and S9) while all other ureas' K_{eq} was measured through exchange/equilibrium (S2-4, S6-8, S10-12) with less bulky ureas on the left column of the table and calculated accordingly. For example. $K_{eq,tBEU} = K_{eq,tBIPU} \times K_{exchange}$.

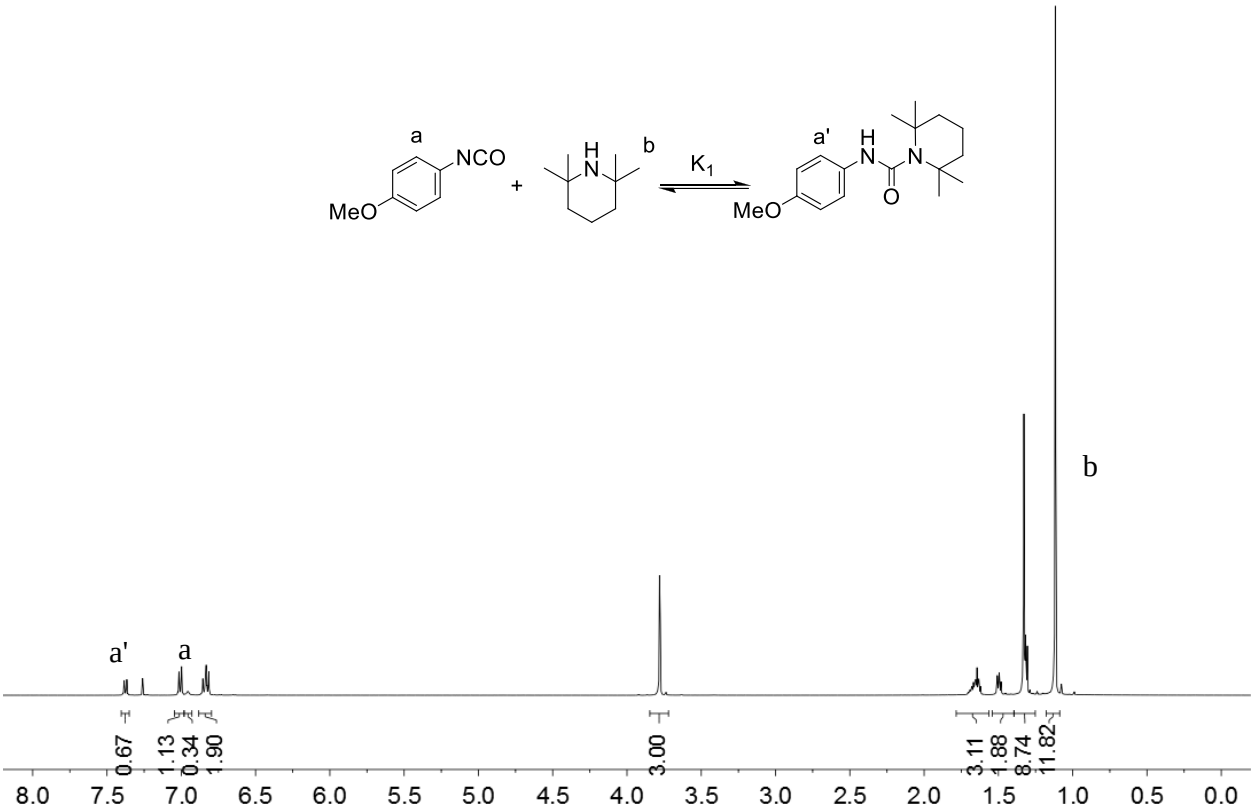


Figure S1. ^{1}H NMR spectrum of equilibrated mixture of 4-methoxylphenyl-isocyanate and tMPCA in $CDCl_3$.

c_0 (NCO)= 0.083 mol/L. K_1(MeO) = [urea]/[NCO][amine]= 0.031/(0.052× 0.046)= 13 M^{-1}

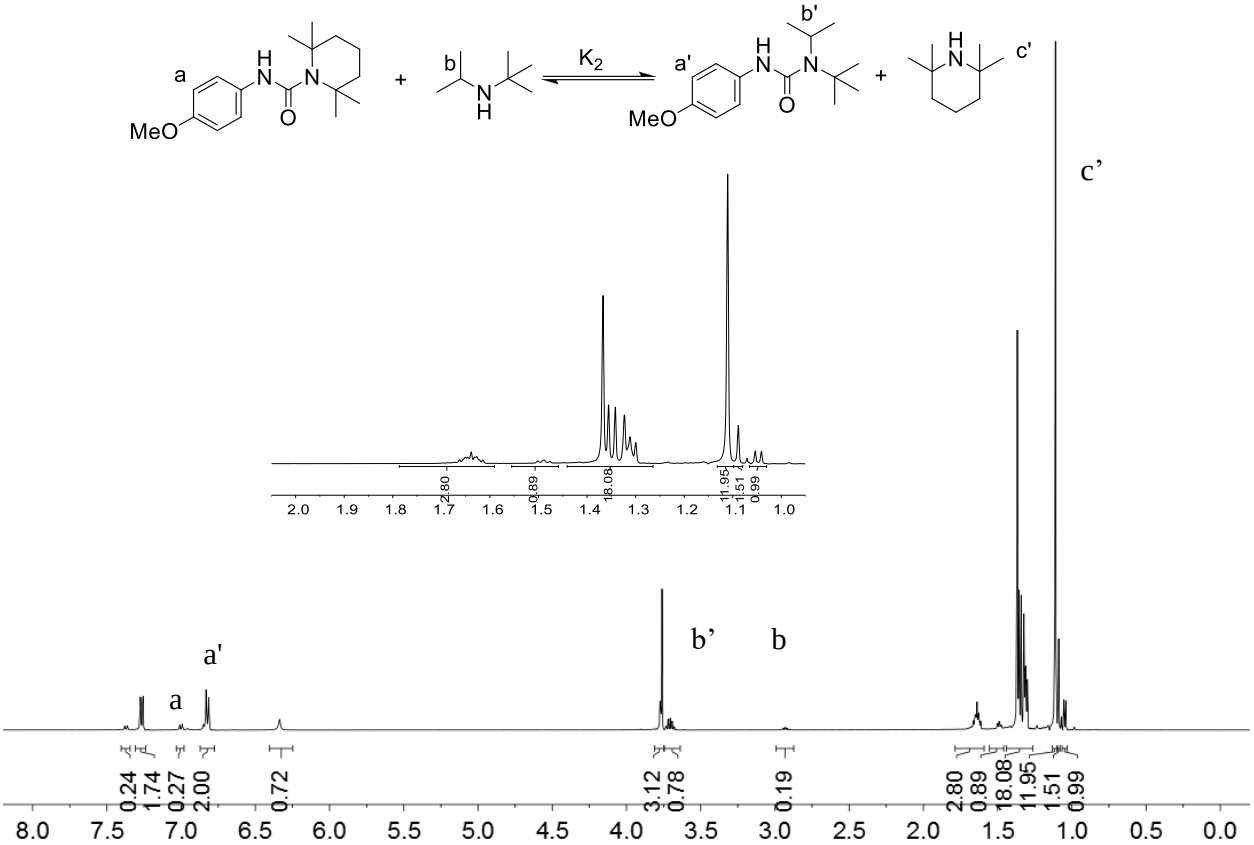


Figure S2. ^{1}H NMR spectrum of equilibrated mixture of MeO-Ph-TMPCU and tBIPA in $CDCl_3$.
K_2(MeO) = ([a’]/2×[c’]/12)/([a]/2×[b]) = 38

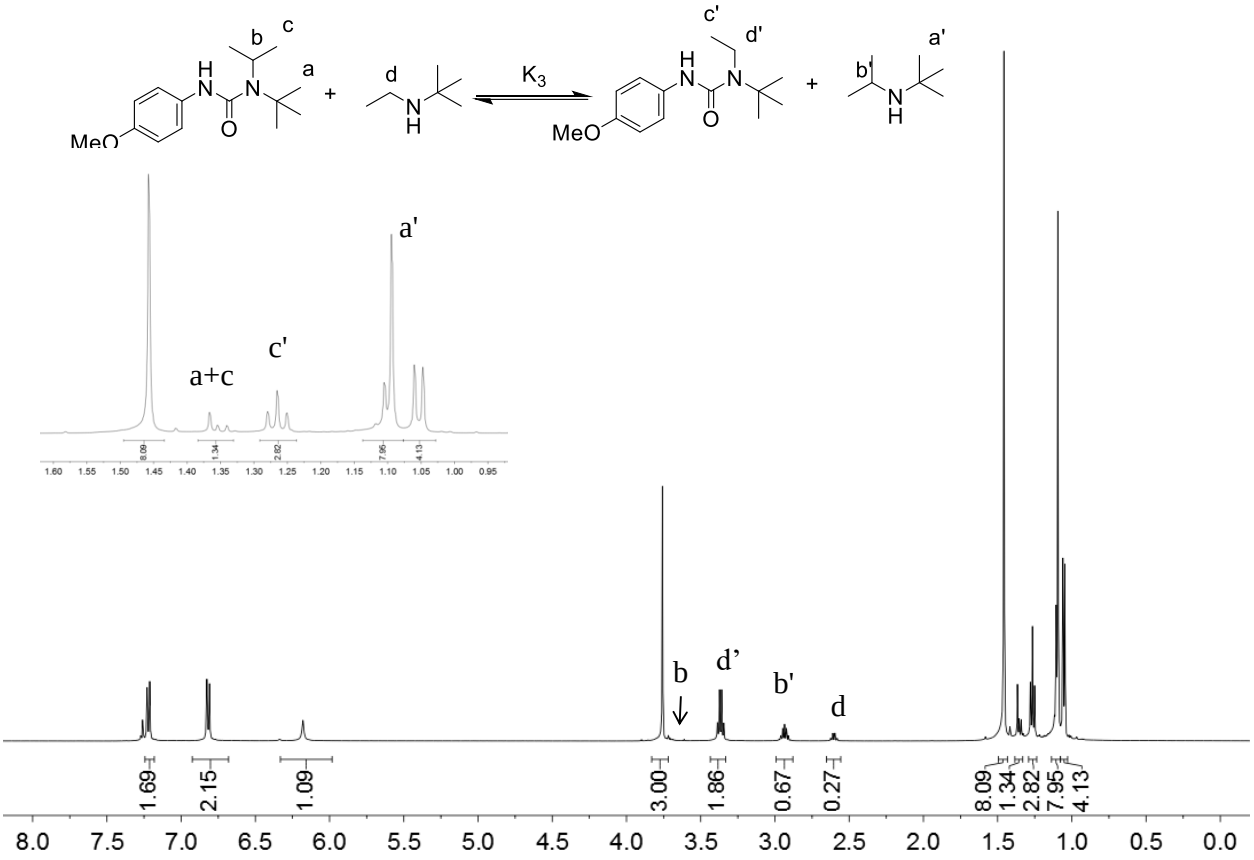


Figure S3. ^{1}H NMR spectrum of equilibrated mixture of MeO-Ph-tBIPU and tBEA in $CDCl_3$.
K_3(MeO) = ([d']/2×[b'])/([a+c]/15×[d]/2) = 56

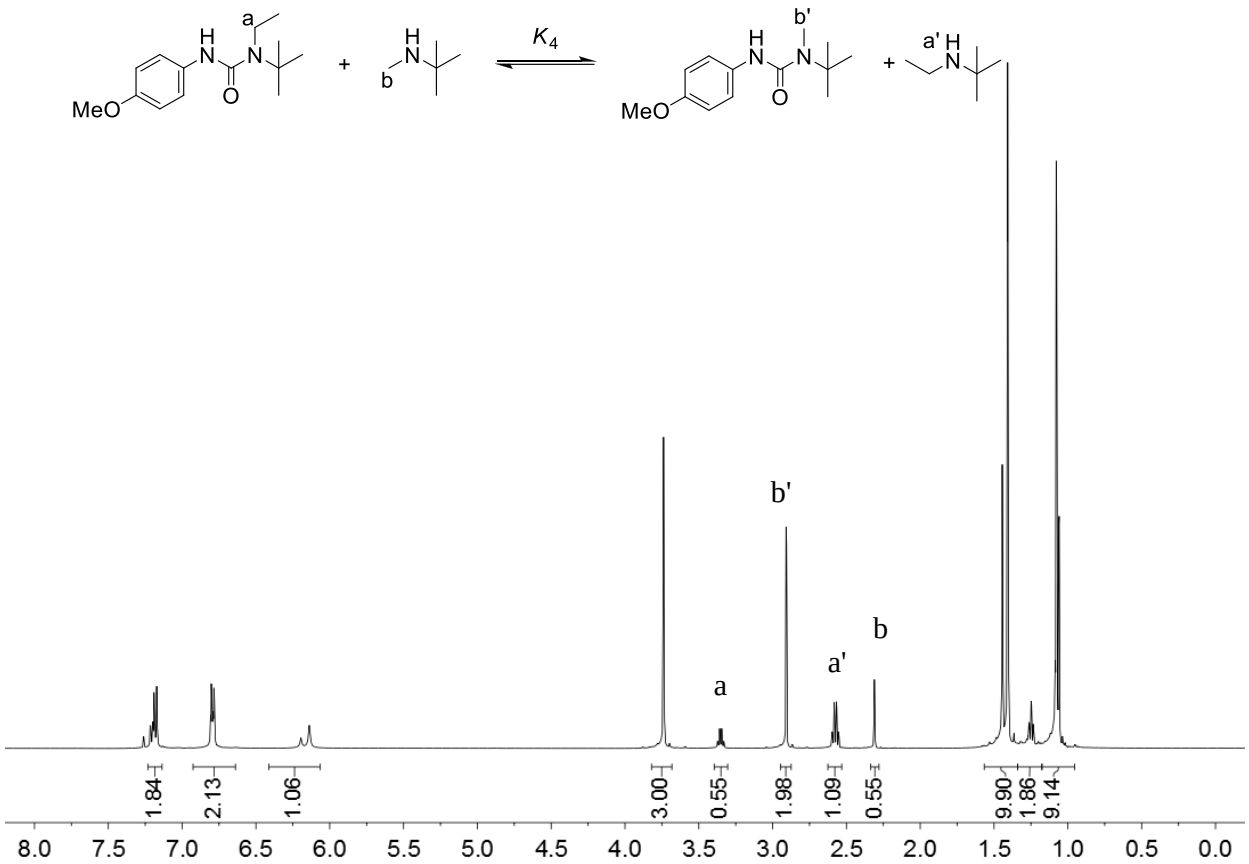


Figure S4. ^{1}H NMR spectrum of equilibrated mixture of MeO-Ph-tBEU and tBMA in $CDCl_3$.
K_4(MeO) = [a'][b']/[a][b] = 1.98×1.09/0.55×0.55 = 7.1

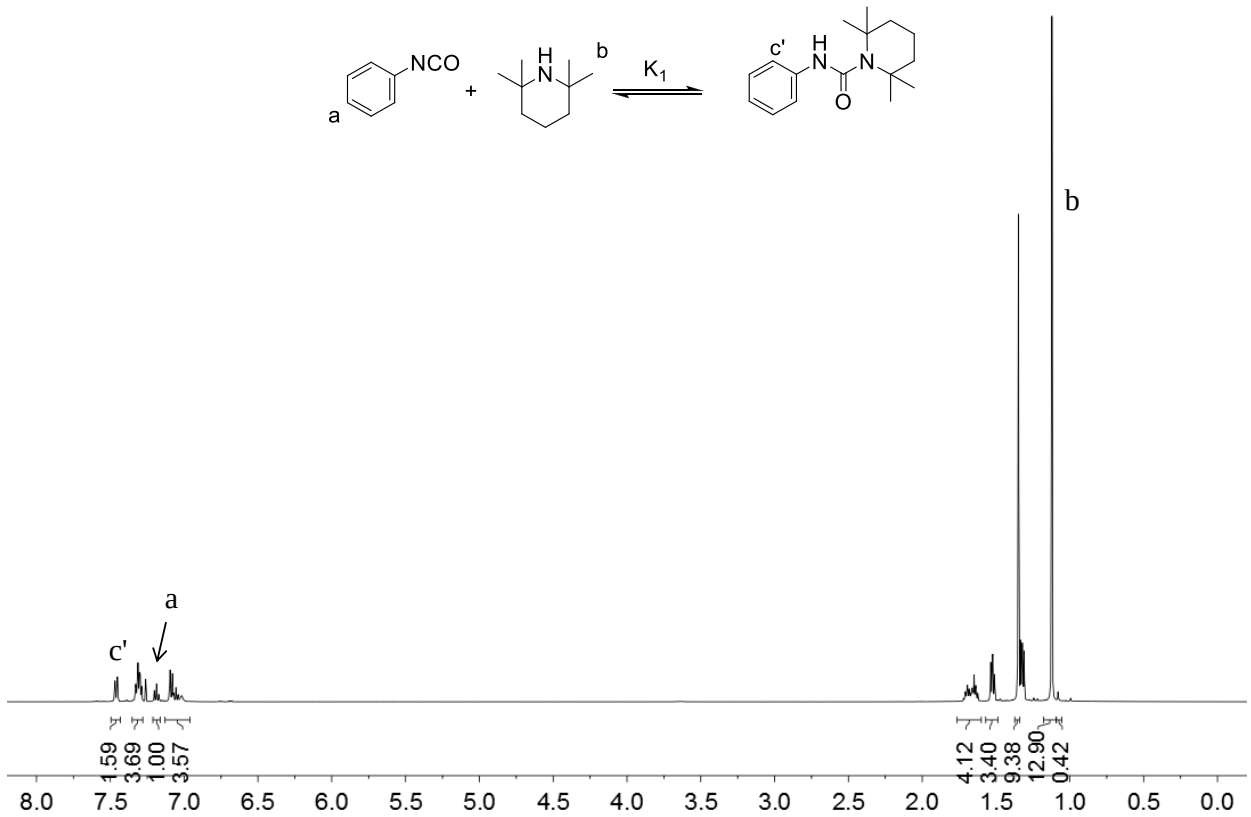


Figure S5. ^{1}H NMR spectrum of equilibrated mixture of phenyl-isocyanate and tMPCA in $CDCl_3$.

c_0 (NCO)= 0.083 mol/L

K_1(Ph) = [urea]/[NCO][amine]= 0.037/(0.046×0.050)= 16 M^{-1}

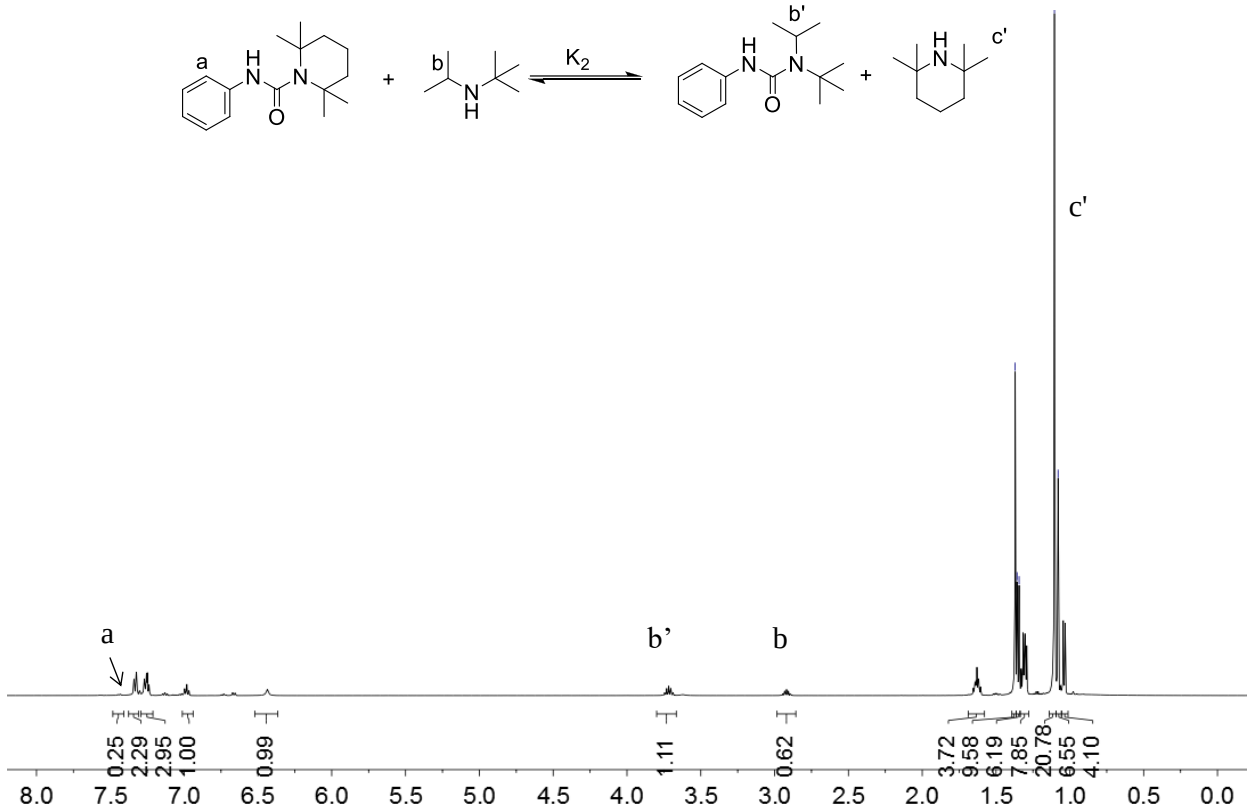


Figure S6. ^{1}H NMR spectrum of equilibrated mixture of Ph-TMPCU and tBIPA in $CDCl_3$.
K_2(Ph) = ([b']×[c']/12)/([a]/2×[b]) = 34

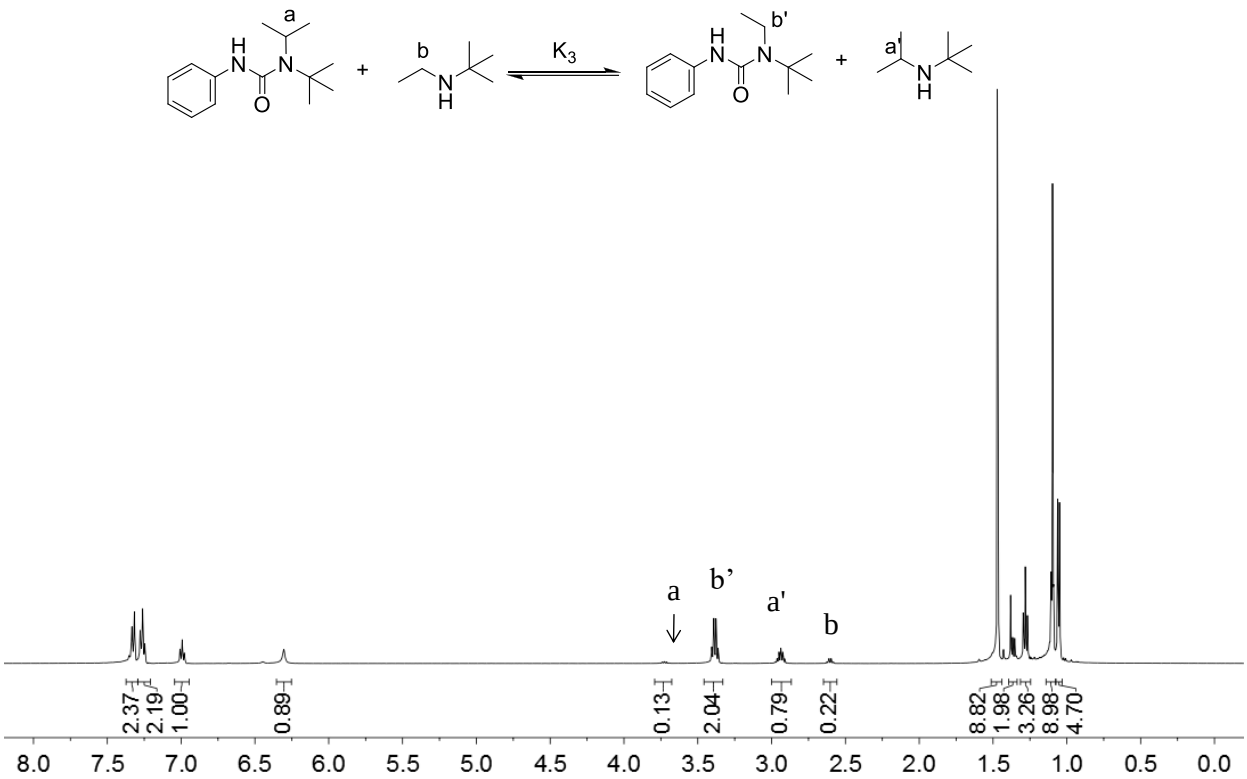


Figure S7. ^{1}H NMR spectrum of equilibrated mixture of Ph-tBIPU and tBEA in $CDCl_3$.
K_3(Ph) = ([b']/2×[a'])/([a]×[b]/2) = 56

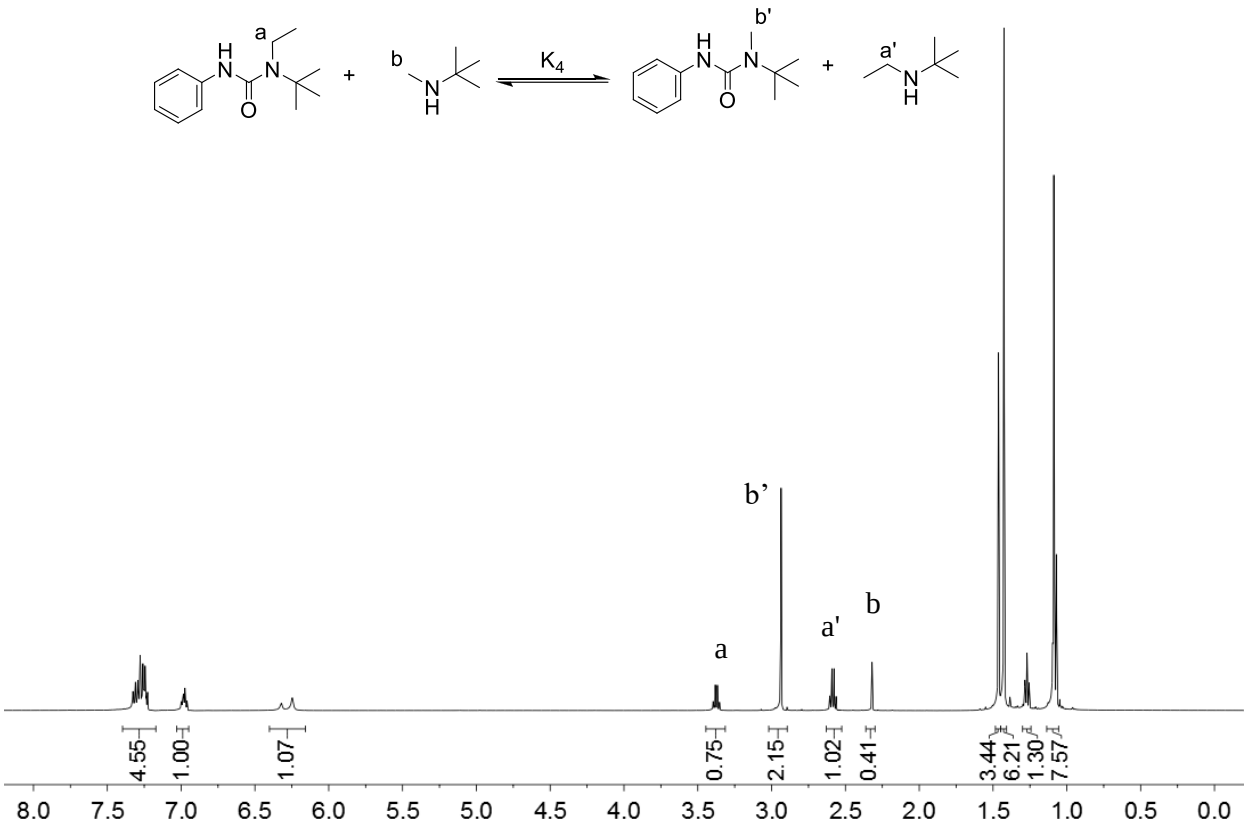


Figure S8. ^{1}H NMR spectrum of equilibrated mixture of Ph-tBEU and tBMA in $CDCl_3$.
K_4(Ph) = ([b’]/3×[a’]/2)/([a]/2×[b]/4) = 7.1

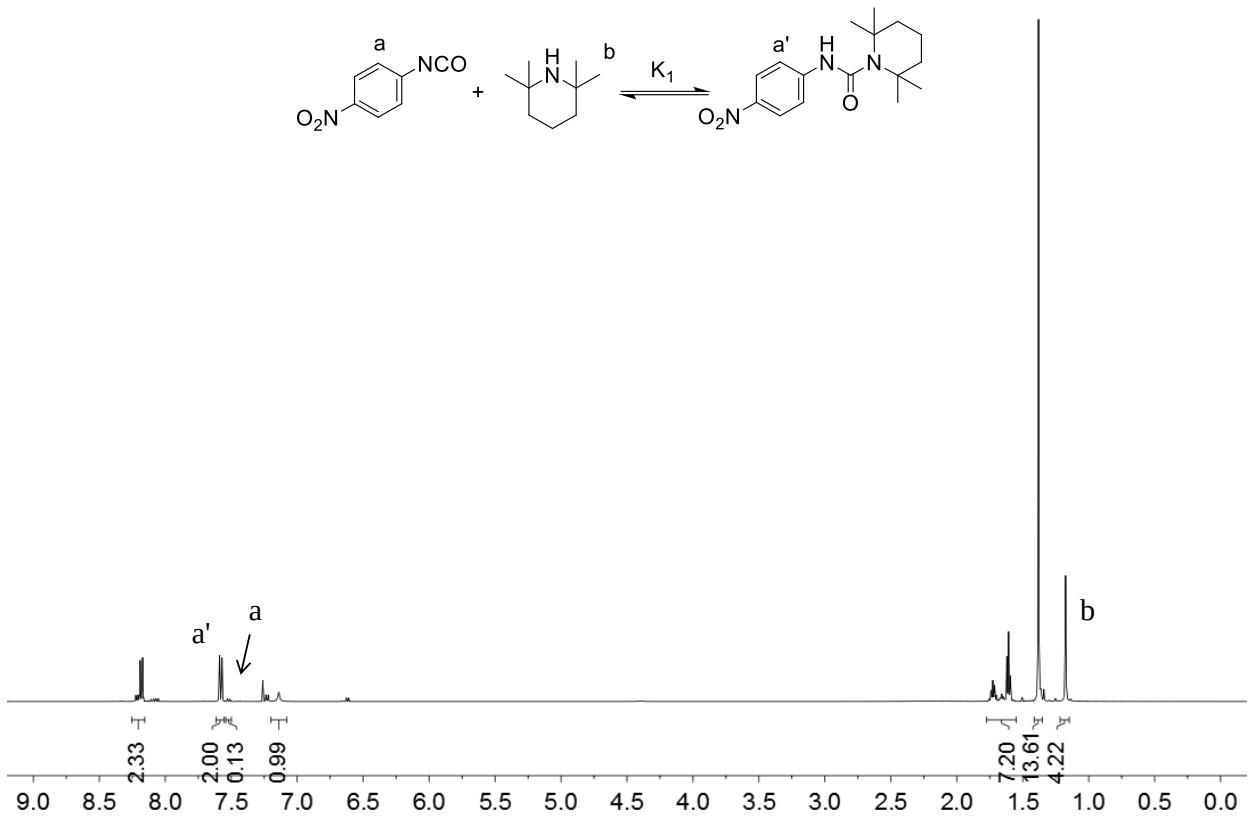


Figure S9. ^{1}H NMR spectrum of equilibrated mixture of 4-nitrophenyl-isocyanate and tMPCA in $CDCl_3$.

c_0 (NCO)= 0.083 mol/L

$K_1(NO_2)$ = [urea]/[NCO][amine]= 0.076/(0.005×0.027) = 5.6×10^2 M^{-1}

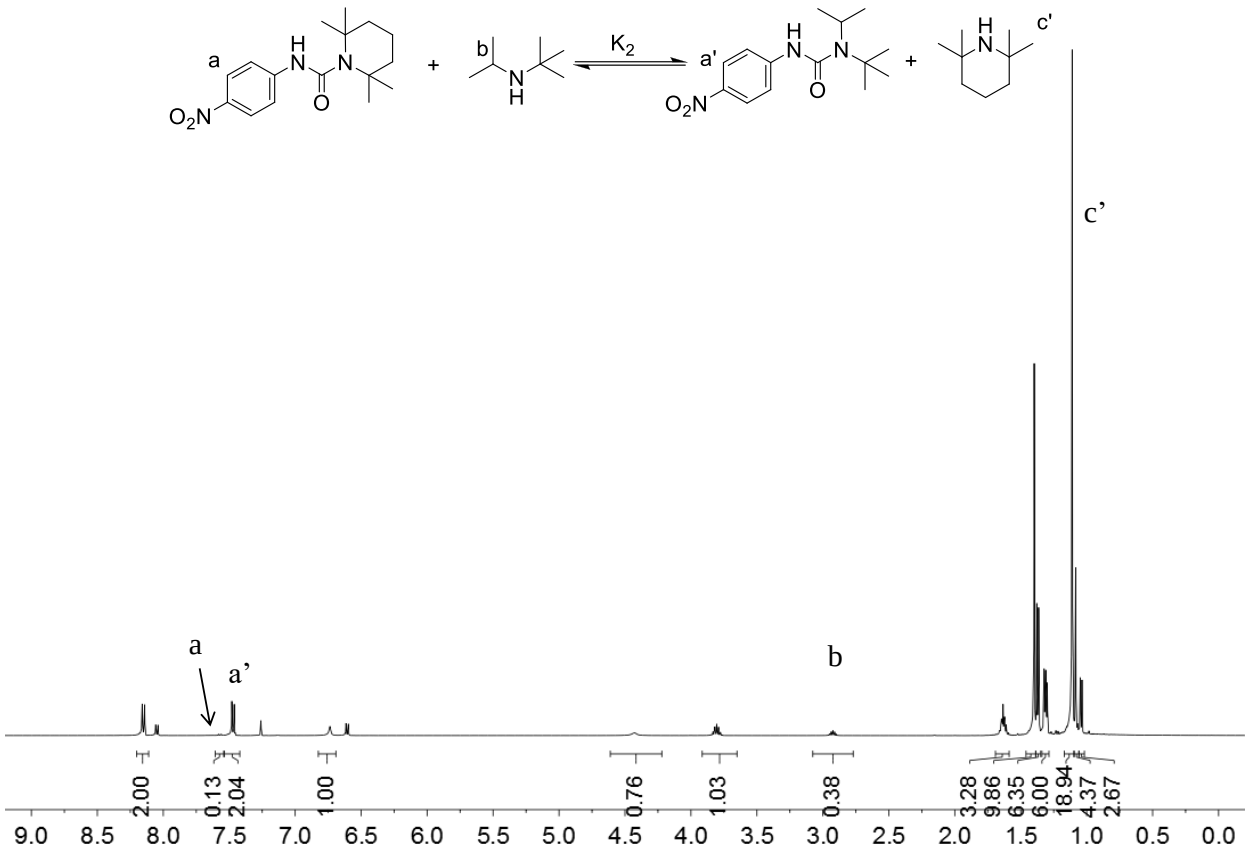


Figure S10. ^{1}H NMR spectrum of equilibrated mixture of NO_2-Ph-TMPCU and tBIPA in $CDCl_3$. $K_2(NO_2)$ = ([a']/2×[c']/12)/([a]/2×[b]) = 65

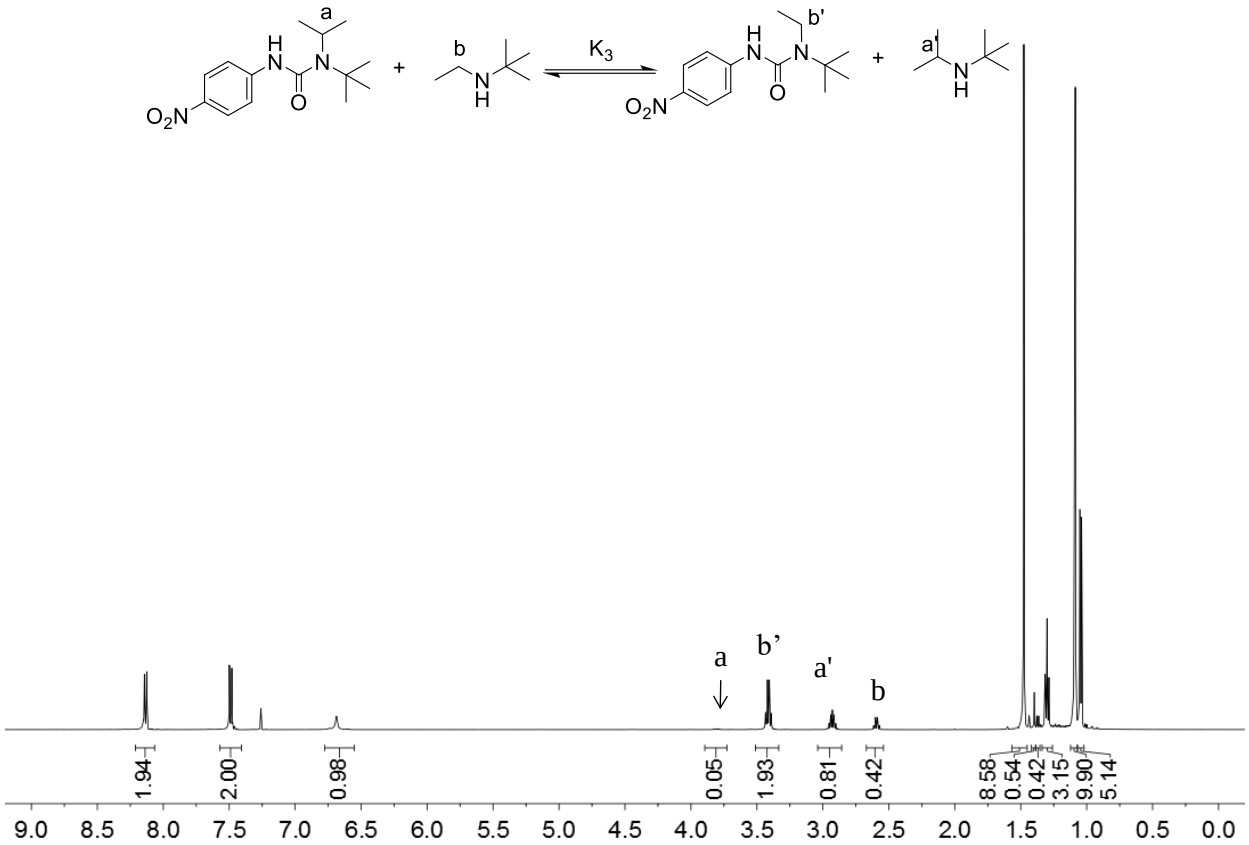


Figure S11. ^{1}H NMR spectrum of equilibrated mixture of NO_2-Ph-tBIPU and tBEA in $CDCl_3$.
$K_3(NO_2)$ = ([b']/2×[a'])/([a]×[b]/2) = 74

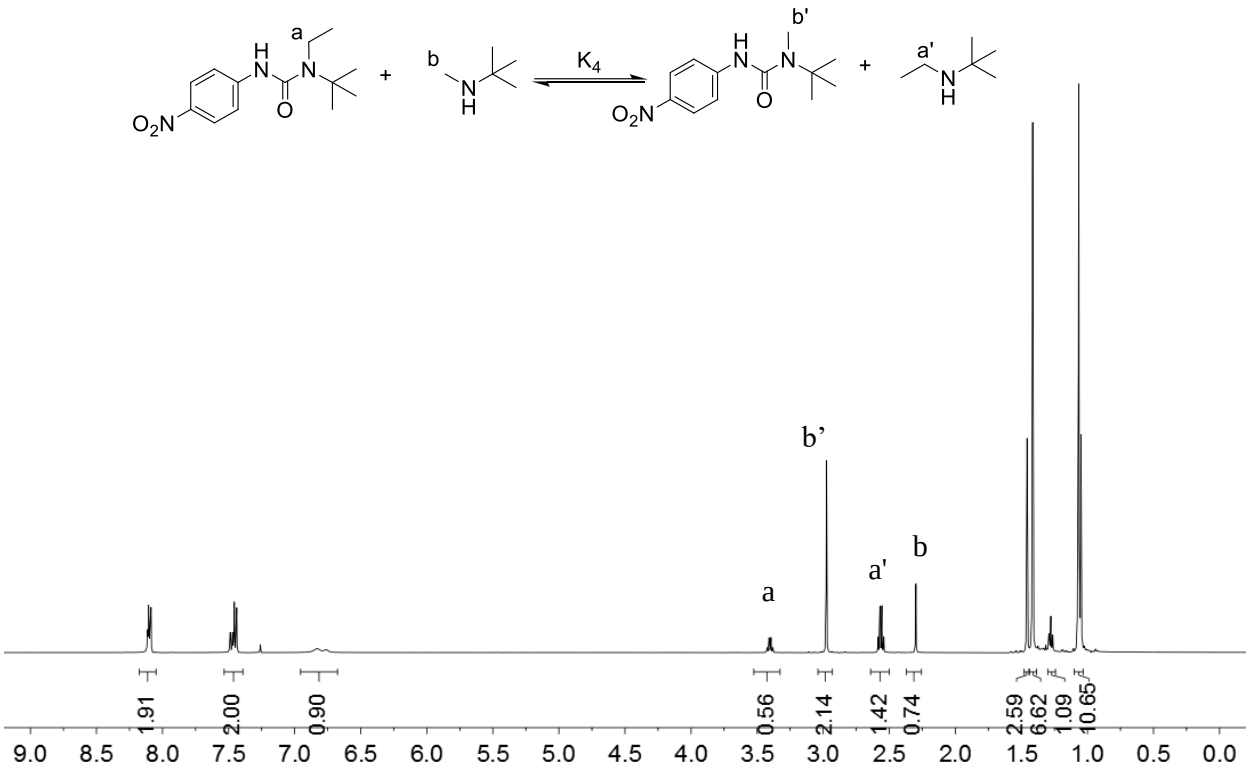


Figure S12. ^{1}H NMR spectrum of equilibrated mixture of NO_2-Ph-tBEU and tBMA in $CDCl_3$.
$K_4(NO_2)$ = ([b']/3×[a']/2)/([a]/2×[b]/4) = 7.3

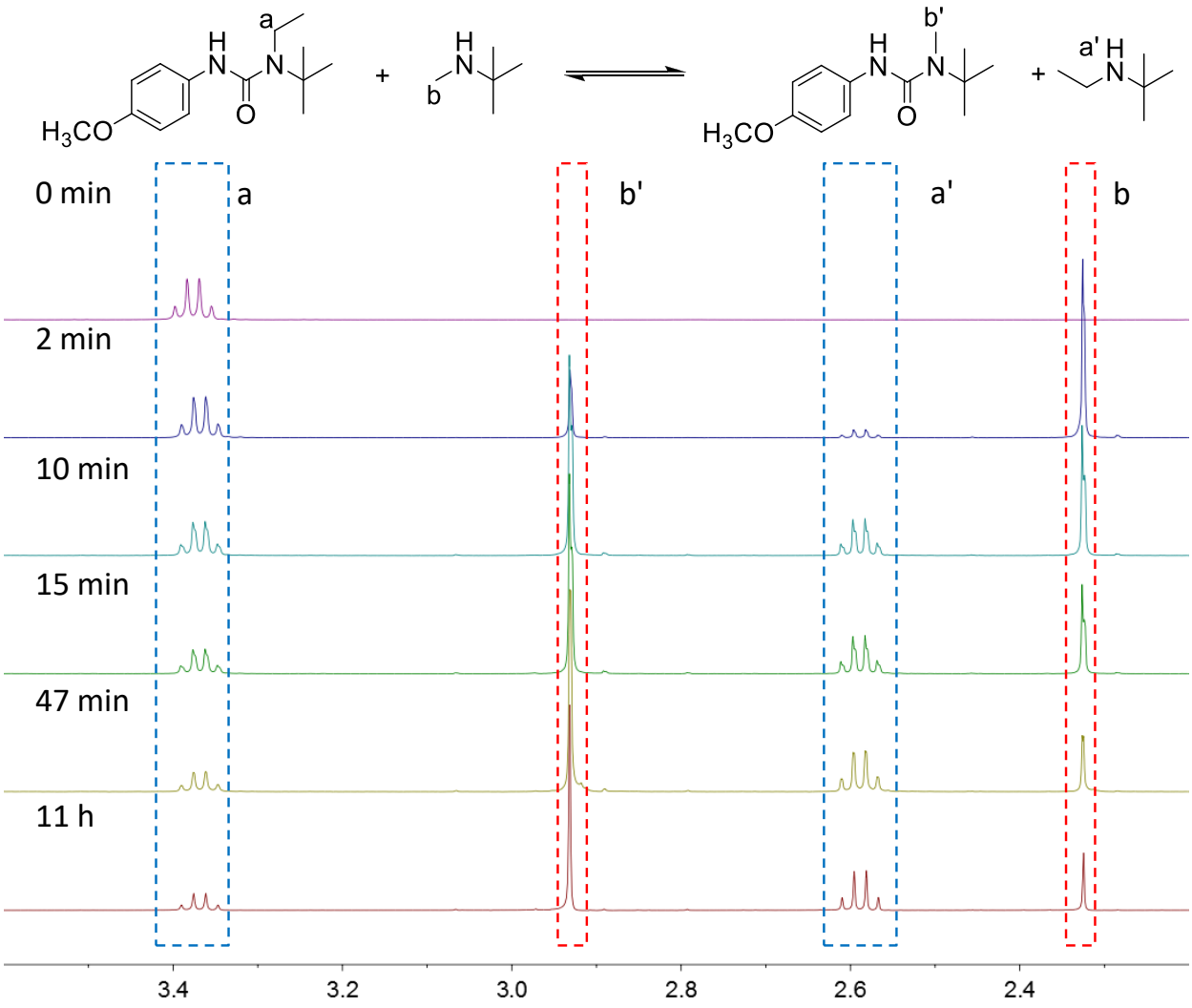


Figure S13. ^{1}H NMR spectrum of the mixture of MeO-Ph-tBEU and tBMU over time in $CDCl_3$

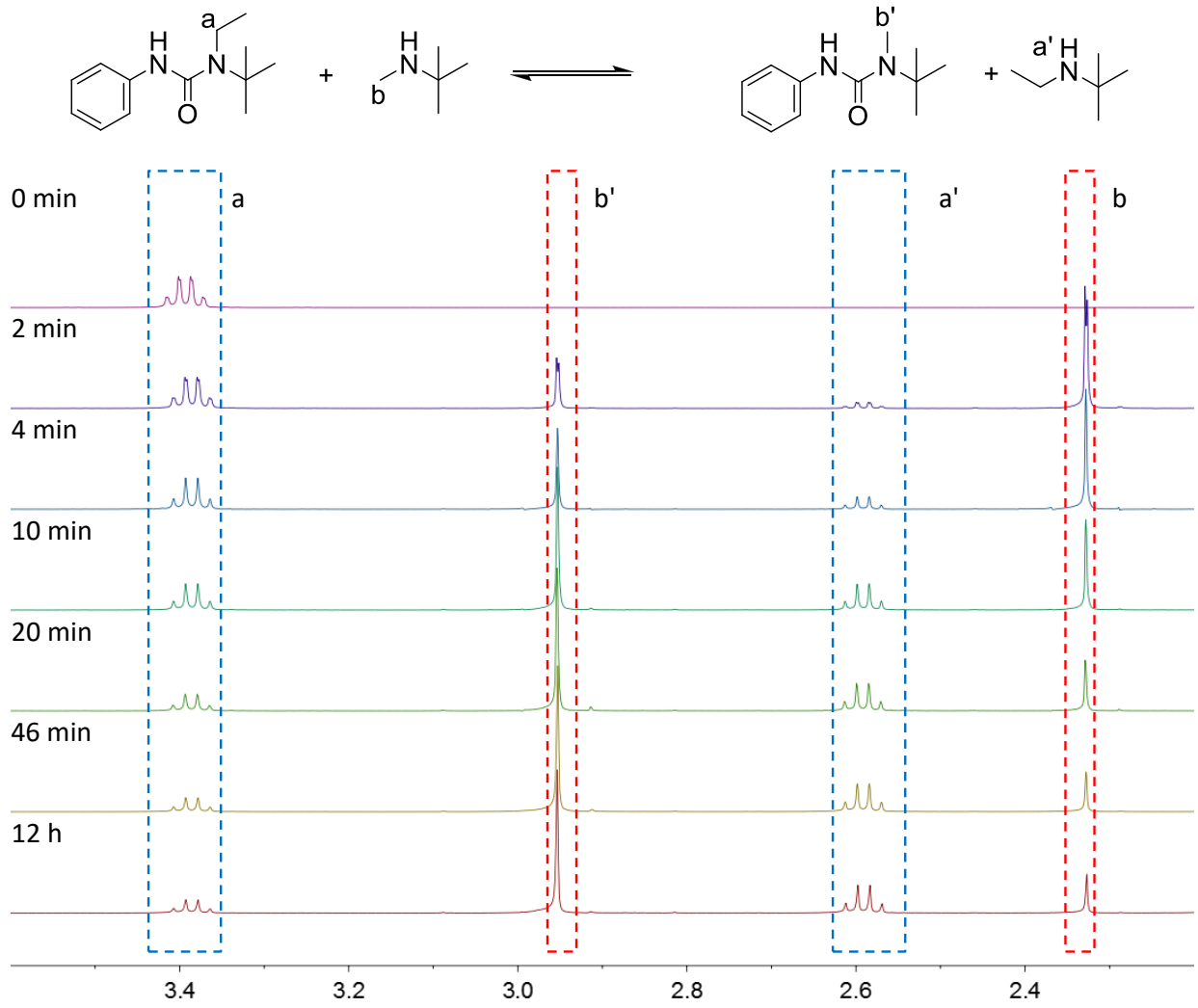


Figure S14. ^{1}H NMR spectrum of the mixture of Ph-tBEU and tBMU over time in $CDCl_3$

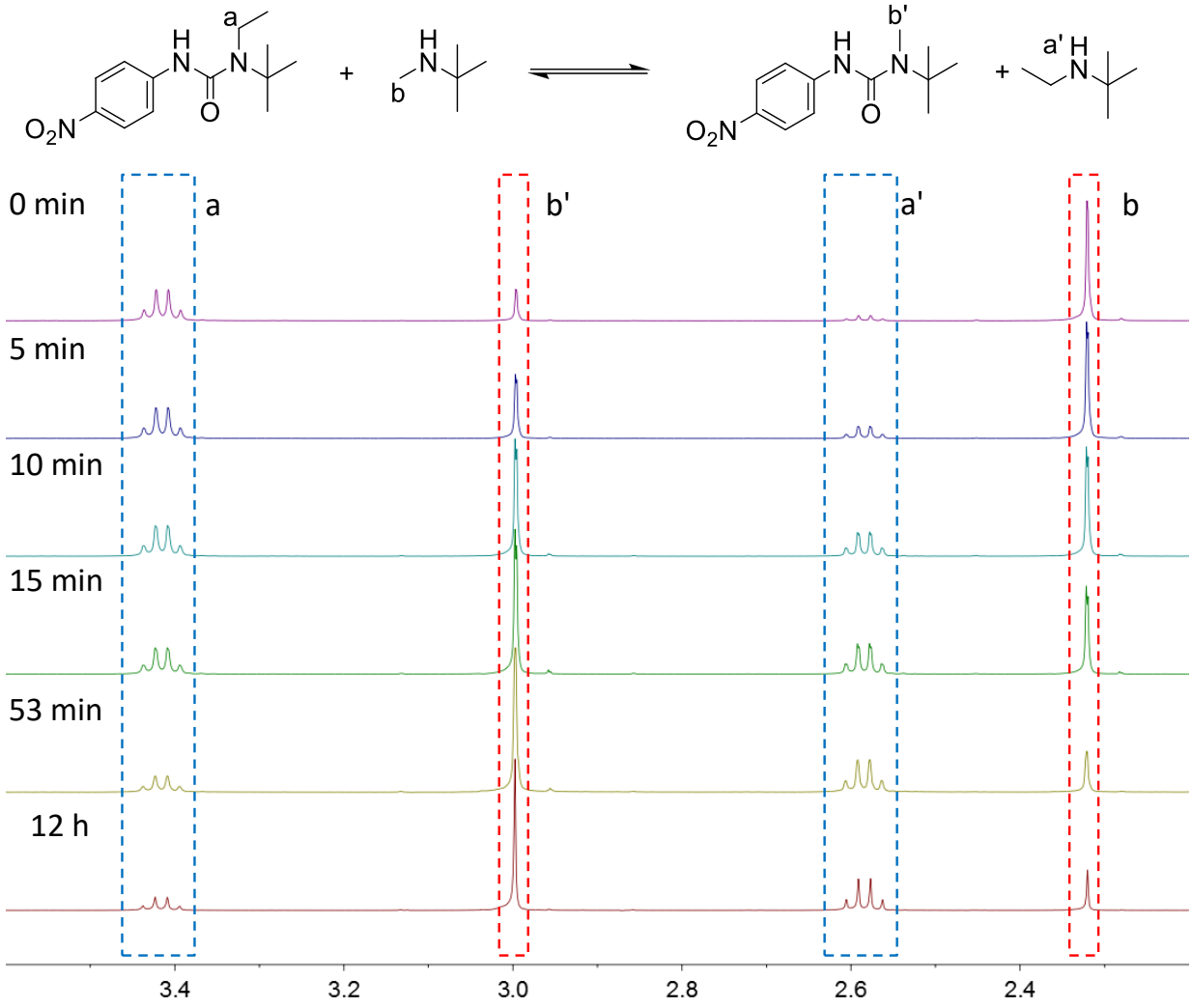


Figure S15. ^{1}H NMR spectrum of the mixture of NO_2-Ph-tBEU and tBMU over time in $CDCl_3$

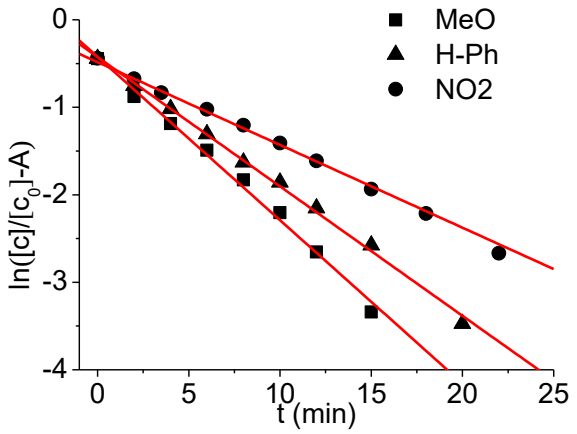


Figure S16. Linear regression of $\ln(\frac{[c_{\mathrm{tBEU}}]}{[c_{\mathrm{tBEU}}]_0} - \mathrm{A}) \sim t$. ($\mathrm{A} = \frac{[c_{\mathrm{tBEU}}]_{\mathrm{eq}}}{[c_{\mathrm{tBEU}}]_0}$) Relative concentration of tBEU was calculated from ^{1}H NMR integration from Figure S13-S15.

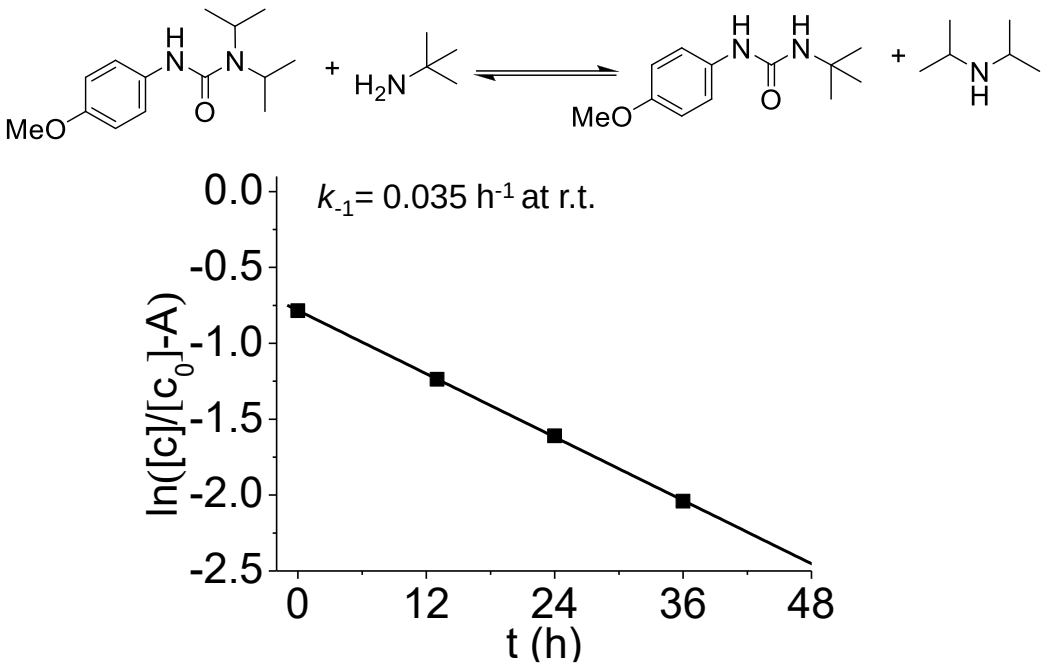


Figure S17. Linear regression of $\ln(\frac{[c_{\mathrm{DIPU}}]}{[c_{\mathrm{DIPU}}]_0} - \mathrm{A}) \sim t$. ($\mathrm{A} = \frac{[c_{\mathrm{DIPU}}]_{\mathrm{eq}}}{[c_{\mathrm{DIPU}}]_0}$) Relative concentration of MeO-Ph-DIPU was calculated from ^{1}H NMR integration.

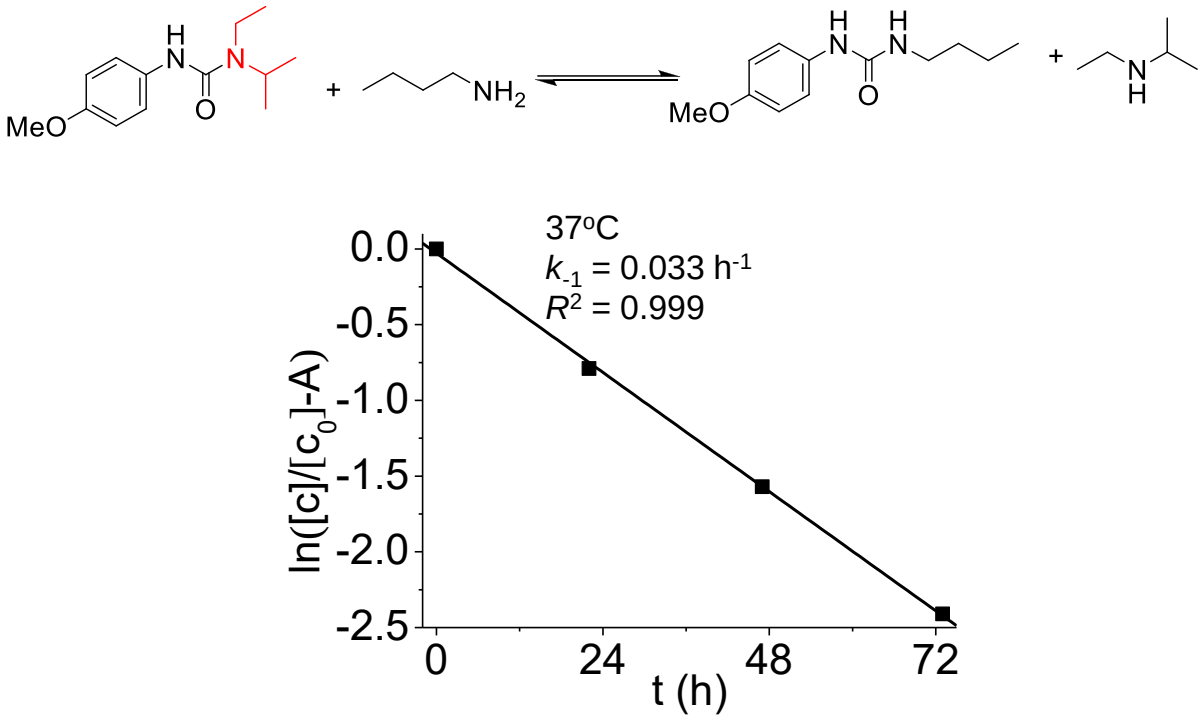
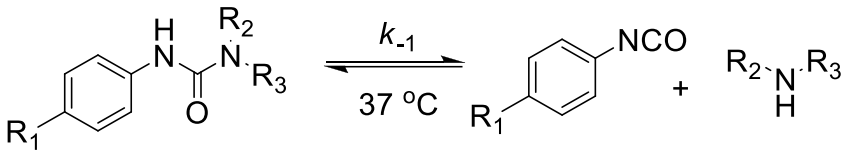


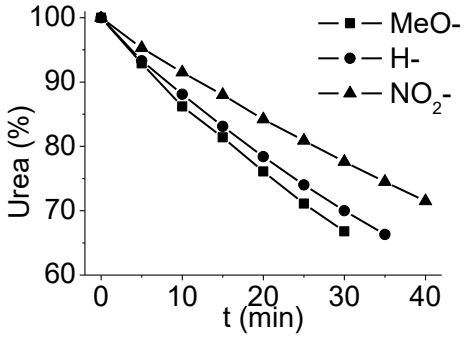
Figure S18. Linear regression of $\ln(\frac{[c_{\mathrm{IPEU}}]}{[c_{\mathrm{IPEU}}]_0} - \mathrm{A}) \sim t$.. ($\mathrm{A} = \frac{[c_{\mathrm{IPEU}}]_{\mathrm{eq}}}{[c_{\mathrm{IPEU}}]_0}$) Relative concentration of MeO-Ph-IPEU was calculated from ^{1}H NMR integration.



R_1	R_2	R_3	*T*	k_{-1}(h^{-1})
MeO	Et	*t*-Bu	25 °C	11.2
H	Et	*t*-Bu	25 °C	8.9
NO_2	Et	*t*-Bu	25 °C	5.7
MeO	*i*-Pr	*i*-Pr	25 °C	0.035
MeO	*i*-Pr	*i*-Pr	37 °C	0.20
H	*i*-Pr	*i*-Pr	37 °C	0.18
NO_2	*i*-Pr	*i*-Pr	37 °C	0.22
MeO	Et	*i*-Pr	37 °C	0.033

Table S2. Summary of dissociation constants of aromatic hindered ureas in *d*-chloroform as measured by ^{1}H NMR.

a)



b)

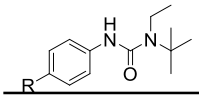
	k_{obs}(h^{-1})	$t_{1/2}$ (h)
MeO-	0.80	0.87
H-	0.70	0.99
NO_2-	0.50	1.39

Figure S19. Hydrolysis of tBEU in d_6-DMSO with 5% H_2O (*v*/*v*) at 37 °C. (a) Hydrolysis kinetics of tBEU with various substitution. (b) Apparent hydrolytic constant and half life of the tBEU.

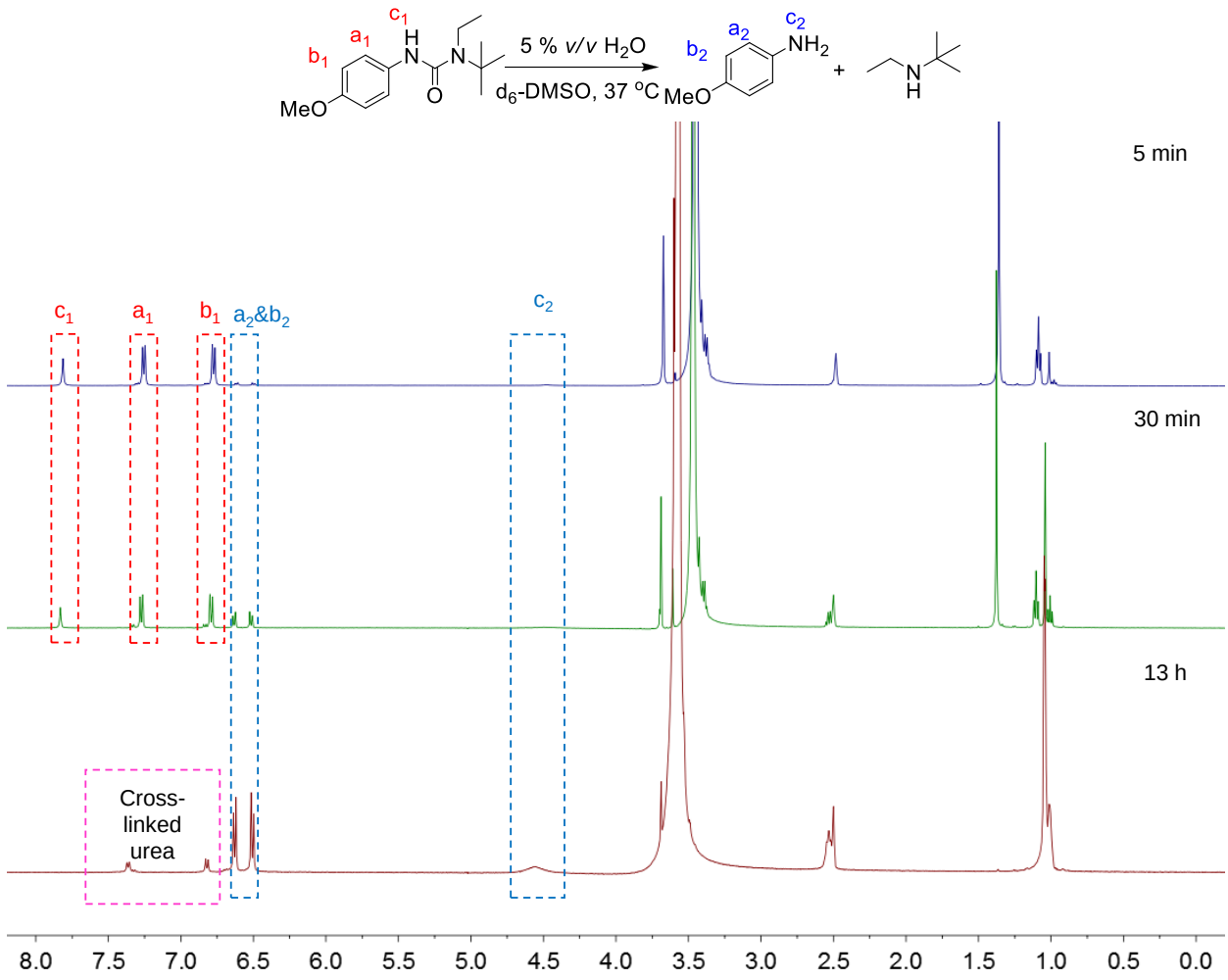


Figure S20. ^{1}H NMR spectrum of MeO-Ph-tBEU in d_6-DMSO with 5% H_2O (v/v) at 37 °C.

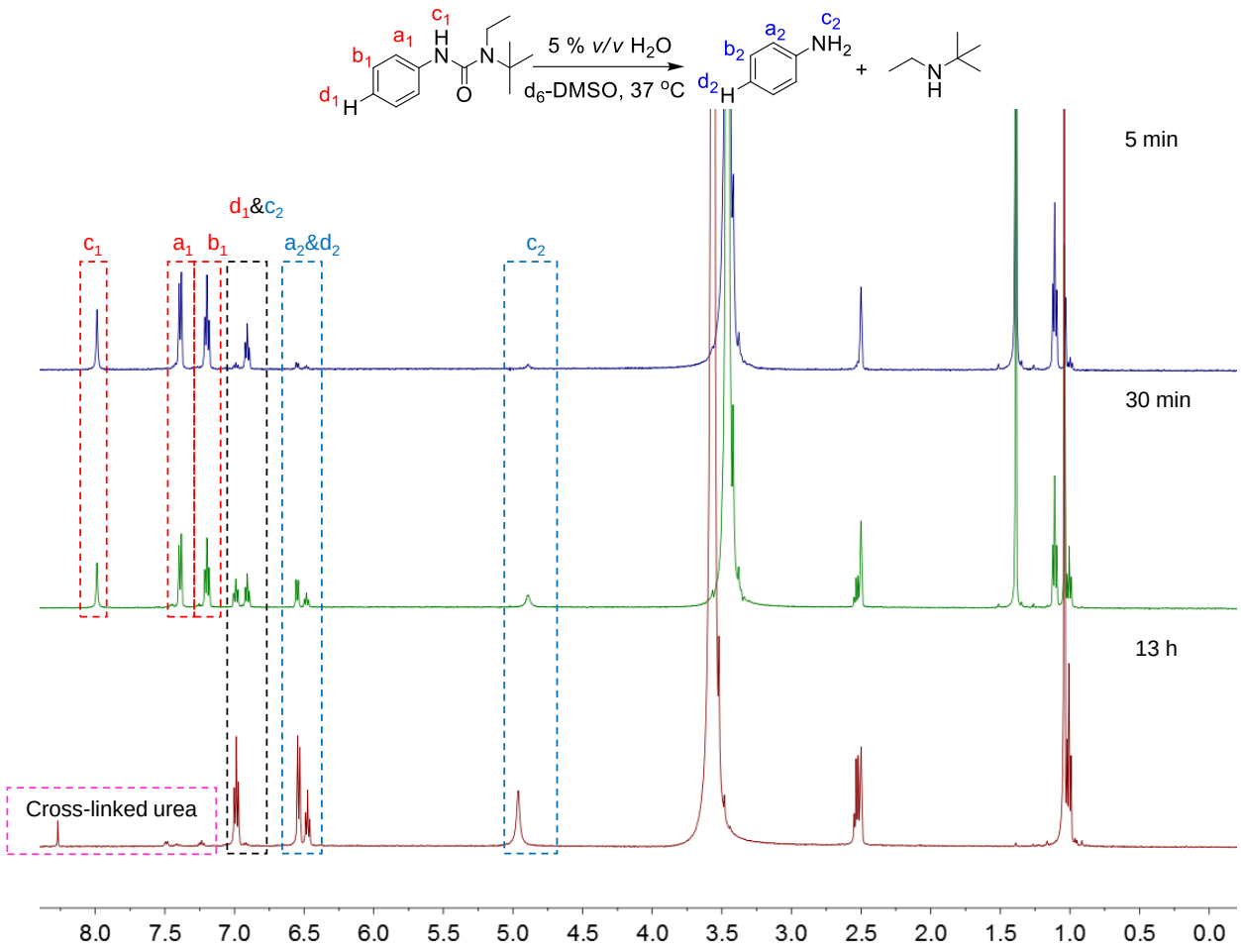


Figure S21. ^{1}H NMR spectrum of Ph-tBEU in d_6-DMSO with 5% H_2O (v/v) at 37 °C.

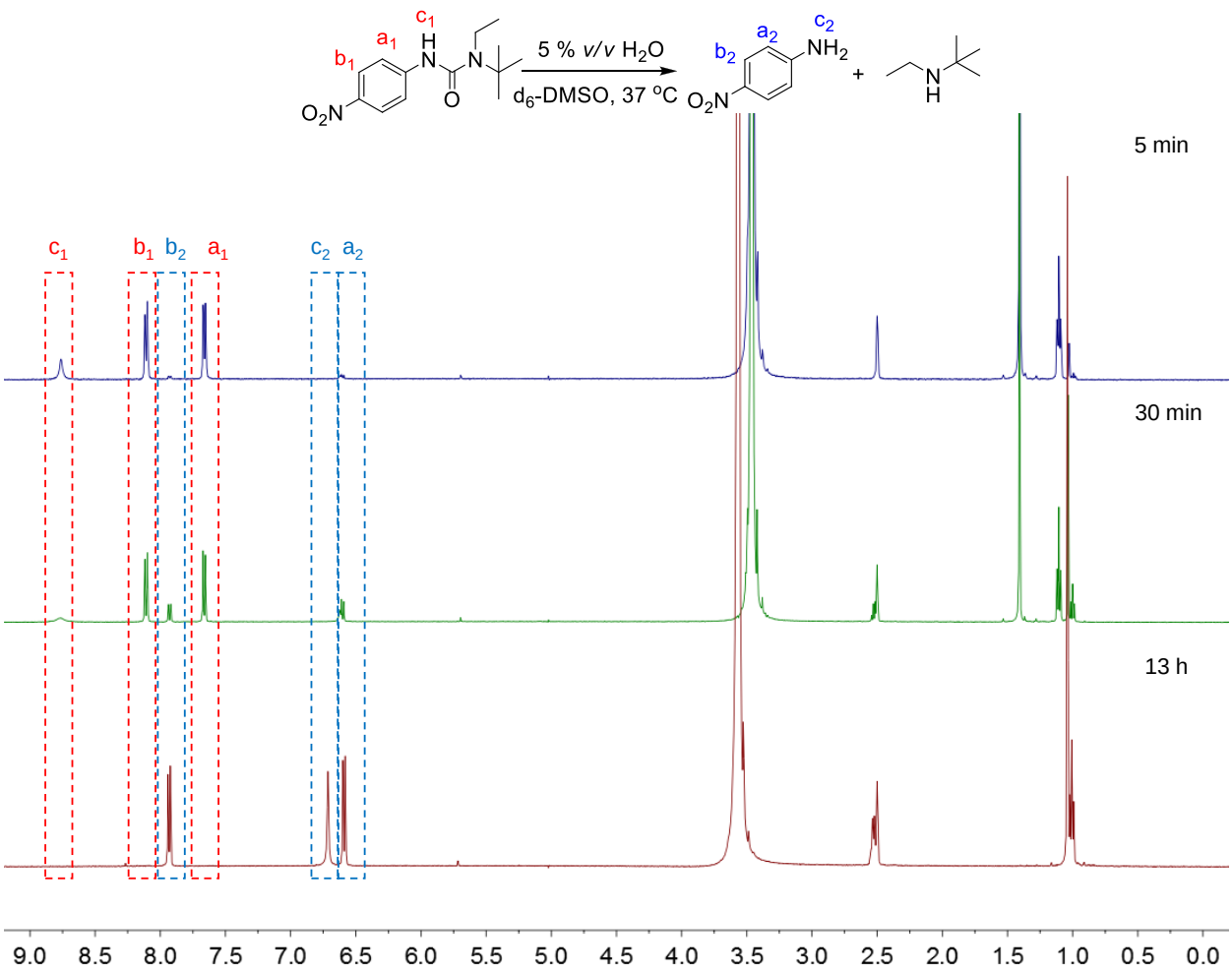


Figure S22. ^{1}H NMR spectrum of NO_2-Ph-tBEU in d_6-DMSO with 5% H_2O (v/v) at 37 °C.

pH	k_{obs} (h^{-1})	R^2
3.0	0.182	0.998
4.0	0.175	0.998
5.0	0.170	0.999
6.0	0.170	0.998
7.0	0.170	0.999
8.0	0.170	0.999
9.0	0.183	0.991
10.0	0.184	0.991
11.0	0.190	0.991
k_{-1}	0.169	0.999

Table S3. Summary of first order hydrolytic constant (k_{obs}) and dissociation constant (k_{-1}) of Ph-tBEU in 1:1 DMSO:buffer at room temperature.

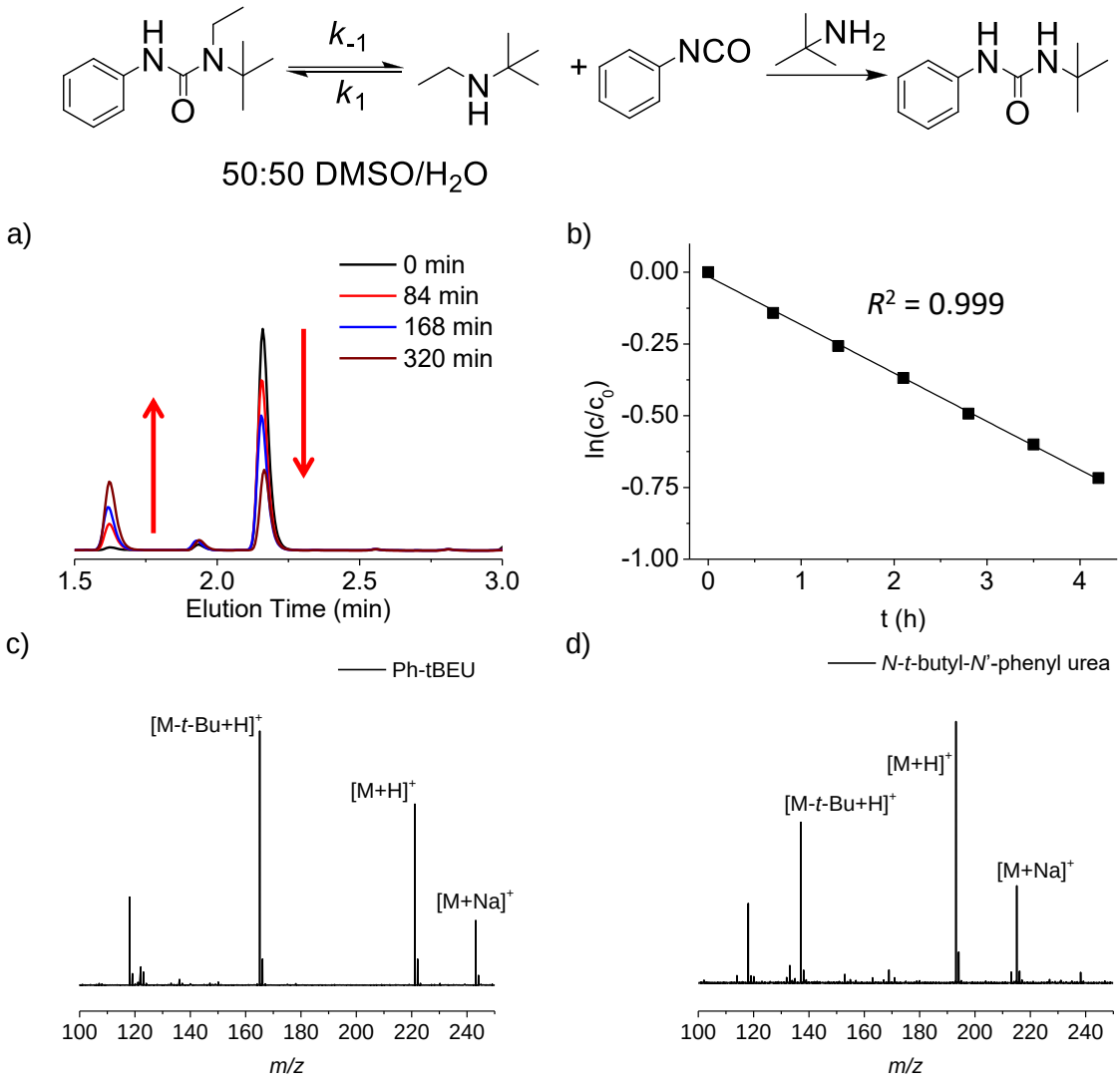


Figure S23. k_{-1} measurement of Ph-tBEU in 50% DMSO-H_2O at 23 °C by HPLC. (a) HPLC trace of the exchange mixture. The rising peak at 1.7 minutes is the *N*-t-butyl-*N*'-phenyl urea and the integrated area matched the consumed Ph-tBEU indicating hydrolysis is negligible in the process. (b) linear regression of the Ph-tBEU concentration over time. The calculated k_{-1} is 0.17 h^{-1}. (c) Mass spectrum of Ph-tBEU characterized by LC-MS. Calculated $[M+H]^+$: 221.1648. Found: 221.1646. (d) (c) Mass spectrum of *N*-t-butyl-*N*'-phenyl urea characterized by LC-MS. Calculated $[M+H]^+$: 193.1335. Found: 193.1335.

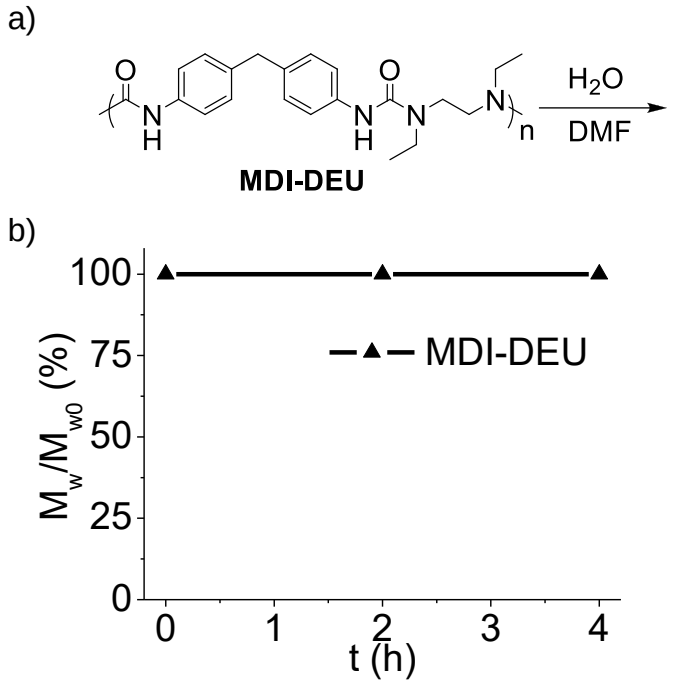


Figure S24. (a) Chemical structure of non-degradable linear polyurea (MDI-DEU). Note that the N-substitution is less bulky than tert-butyl group and the polymer is much less dynamic than MDI-tBEU. (b) Relative molecular weight change of MDI-DEU in 5% H_2O-DMF solution at 37 ^oC.

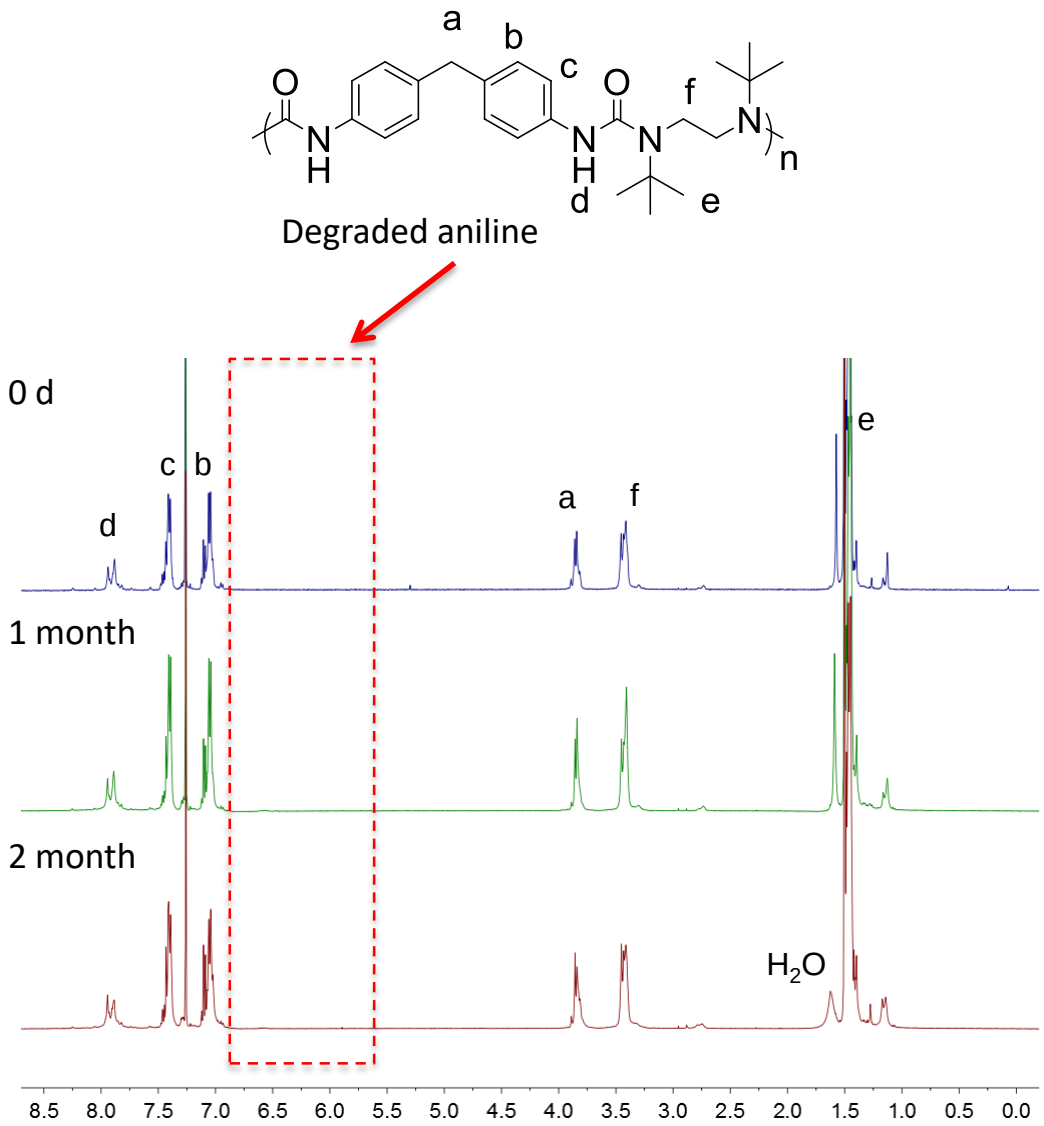


Figure S25. ^{1}H NMR ($CDCl_3$) of MDI-tBEU powder stored in glass vial under ambient condition.. No degraded aniline was observed in aromatic region (δ 6.5-6.8 ppm).

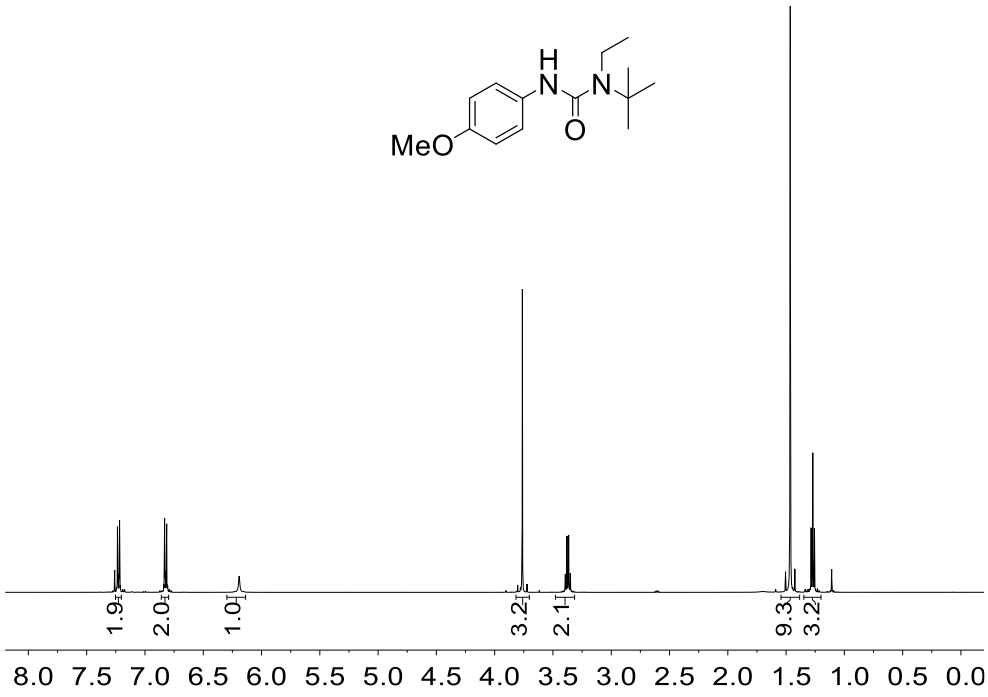


Figure S26. ^{1}H NMR of MeO-Ph-tBEU in $CDCl_3$.

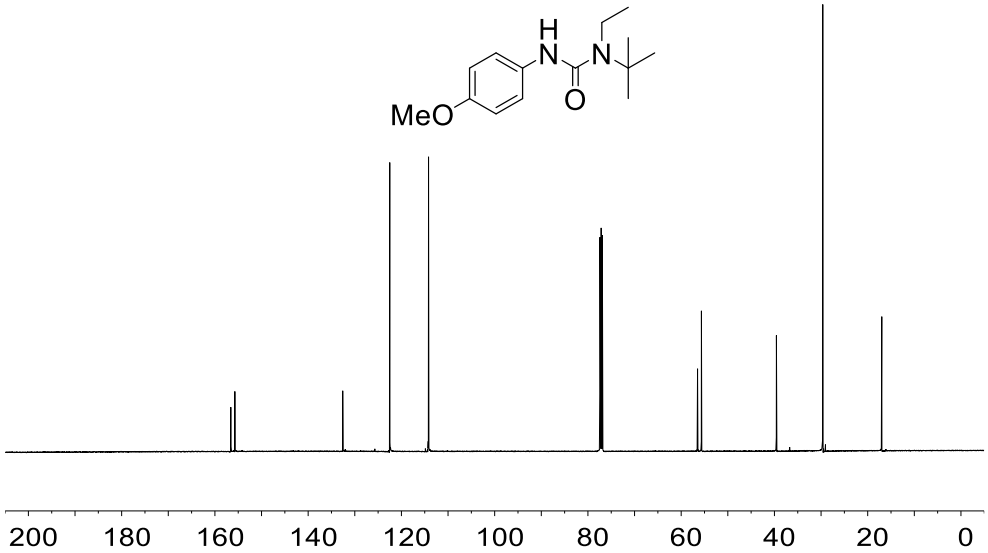


Figure S27. ^{13}C NMR of MeO-Ph-tBEU in $CDCl_3$.

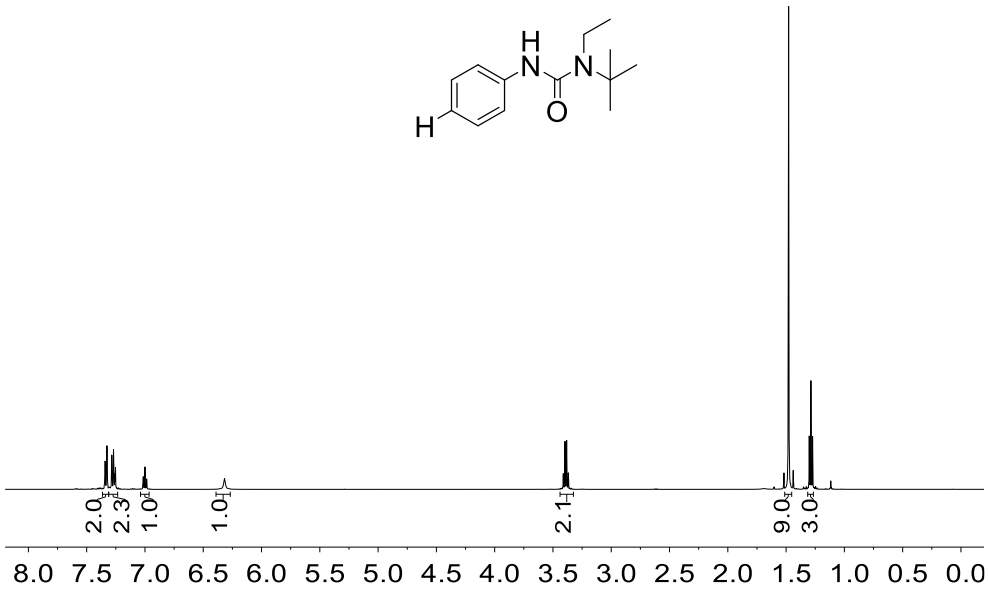


Figure S28. ^{1}H NMR of Ph-tBEU in $CDCl_3$.

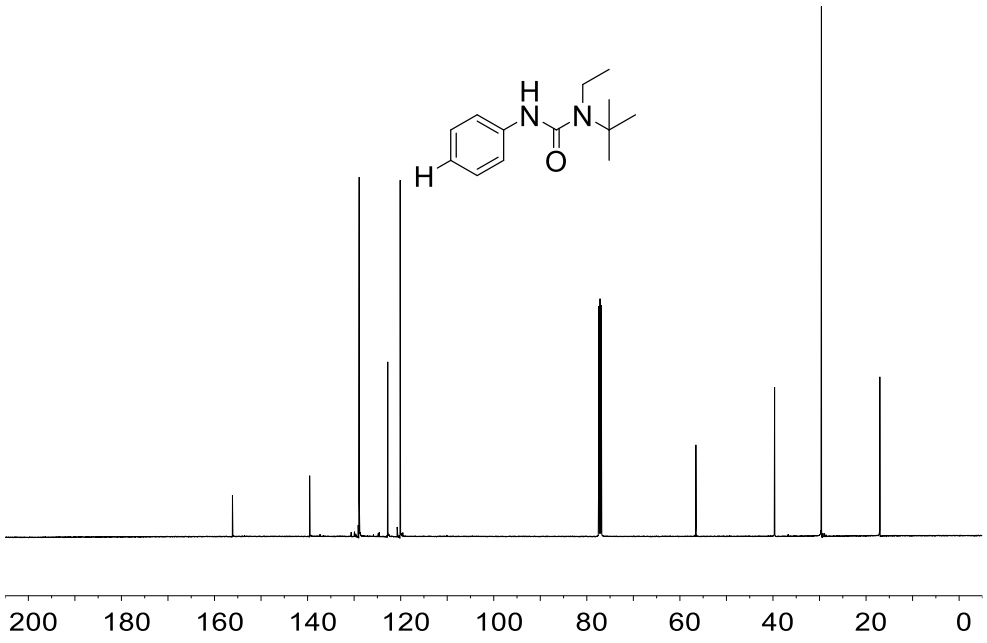


Figure S29. ^{13}C NMR of Ph-tBEU in $CDCl_3$.

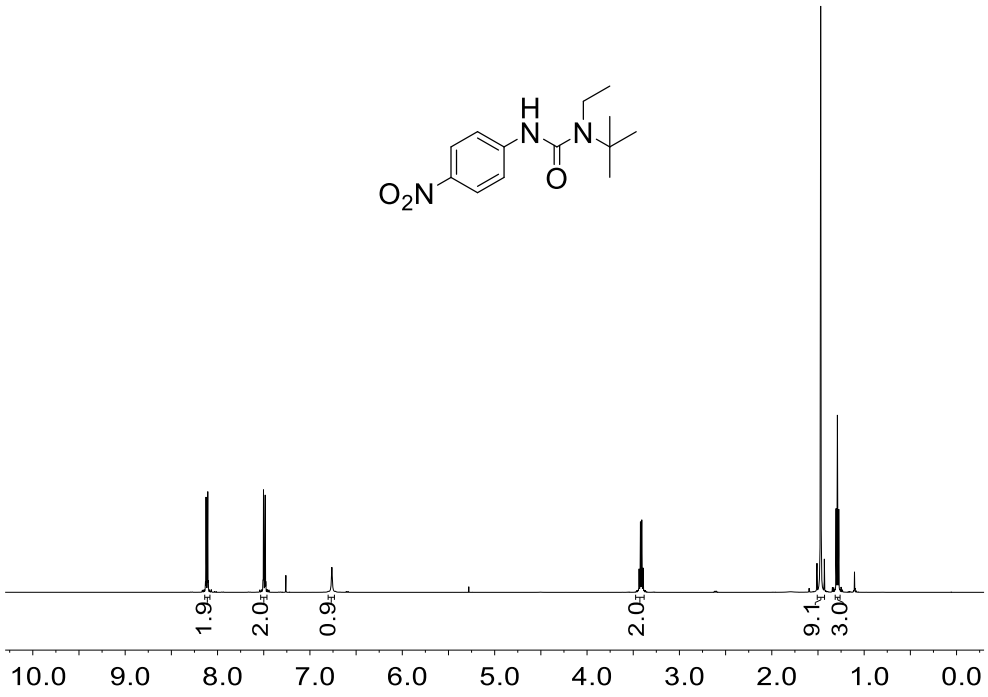


Figure S30. ^{1}H NMR of NO_2-Ph-tBEU in $CDCl_3$.

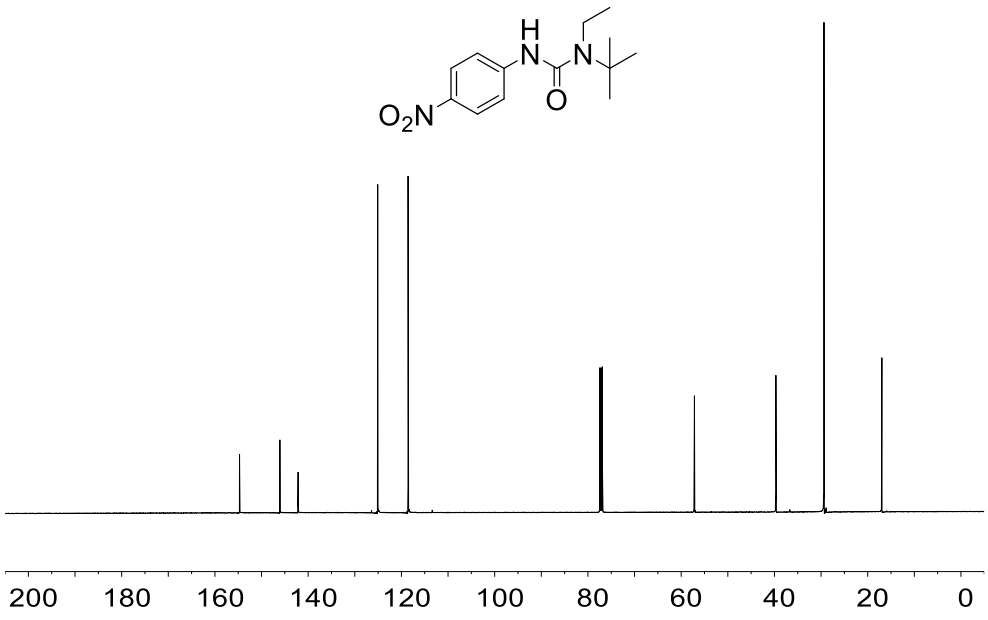


Figure S31. ^{13}C NMR of NO_2-Ph-tBEU in $CDCl_3$.

Reference

(1) (a) Ying, H.; Zhang, Y.; Cheng, J. *Nat. Commun.* **2014**, *5*, 3218. (b) Ying, H.; Cheng, J. *J. Am. Chem. Soc.* **2014**, *136*, 16974-16977.