Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions

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To the memory of Professor Jose Barluenga, a pioneer and an innovator in organometallic chemistry

Abstract: *Shattering the long-held dogma that organolithium chemistry needs to be performed under inert atmospheres in toxic organic solvents, chemoselective addition of organolithium reagents to non-activated imines and quinolines has been accomplished in Green, biorenewable Deep Eutectic Solvents (DESs) at room temperature and in the presence of air, establishing a novel sustainable access to amines. Improving on existing methods, this approach proceeded in the absence of additives; occurred without competitive enolization, reduction or coupling processes; and reactions were completed in seconds. Comparing RLi reactivities in DESs with those observed in pure glycerol or THF suggests a kinetic anionic activation of the alkylating reagents occurs, favouring nucleophilic addition over competitive hydrolysis.*

Nucleophilic addition of organolithium derivatives to carbonyl compounds (e.g., ketones or aldehydes) is a common methodology to access new C-C bonds allowing synthesis of functionalized alcohols.[1] Contrastingly, their use as nucleophiles to transform imines to amines via direct 1,2-addition processes has been significantly less developed.[2] Reduced electrophilicity of the C=N group, competitive abstraction of acidic α-Hs to give azaenolates and possible formation of reductive coupling side-products are some mitigating factors, which can compromise the chemoselectivity of this approach.[3] Strategies undertaken to overcome these limitations include the use of Lewis acids (e.g., $AlMe_3$, LiBr)[4,5] as additives that can activate the organic substrate and of alternative alkylating reagents such as magnesium zincates ([MgCl][ZnR_3]) which appear more chemoselective than conventional common RLi or RMgX reagents.[1,2] However, all these protocols, as with nearly all methods using polar organometallics, require restrictive reaction conditions. This includes use of inert atmospheres, dry oxygen-free organic solvents and in many cases low temperatures (-78 ºC) in order to avoid intermediate degradation and side reactions.[6] Thus, running polar organometallic chemistry under aerobic and/or hydrous conditions is the ultimate challenge to synthetic chemists.[7] As an opening gambit towards this target, we recently pioneered use of green and biorenewable Deep Eutectic Solvents (*DESs*) combining ammonium salt choline chloride (*ChCl*) with water or glycerol (*Gly*) (Fig. 1) showing they can activate Grignard and organolithium reagents to promote room temperature chemoselective ketone alkylation/arylation reactions.[8] Moreover, air could be tolerated in these additions. Subsequent insightful studies by Capriati reported lithiation of diaryltetrahydrofurans in *ChCl*-based *DESs* under air, finding it competitive with protonolysis as well as RMgX and RLi mediated-additions to γ-chloroketones to furnish 2,2-disubstituted tetrahydrofurans.[9] Taking organolithium *DES* chemistry into new, more taxing territory, here we describe the chemoselective addition of organolithium compounds to both imines and quinolines in *DESs* under air as a novel sustainable methodology to amines. This has wide implications as amine synthesis has been identified as a key area in Green Chemistry for pharmaceutical manufacturers.[10]

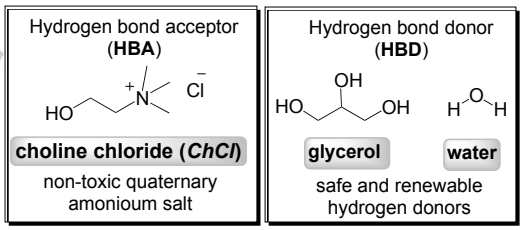

Figure 1: Components of *DES* mixtures used in this study.

This study examined adding RLi reagents to a range of imines at room temperature, in air, using *DESs* as solvents.[11] The scope of this Green approach considered: (i) the *DES* combination, (ii) the organometallic reagent; and (iii) the imine. Firstly we assessed the reaction of commercially available ^{n}BuLi with aromatic imine *N*-Benzylideneaniline (**1a**) using different stoichiometries [entries 1-4, Table 1] in the eutectic mixture 1*ChCl*/2*Gly*. Remarkably, under conditions incompatible with conventional organolithium chemistry, almost quantitative formation of amine (**2a**) was observed employing only slight excess of ^{n}BuLi (1.4 equiv., entry 2), in a very short reaction time (2-3 seconds). Advantages of this approach are that: (i) no additives are required to achieve high conversions; (ii) competitive enolization, reduction or coupling reactions were not observed;[12] (iii) edging closer to stoichiometric conditions, a slight excess of ^{n}BuLi gave full conversion to the desired amine **2a**, even though hydrolysis could be expected in the protic solvent; and (iv) no imine decomposition was seen in the eutectic mixture.

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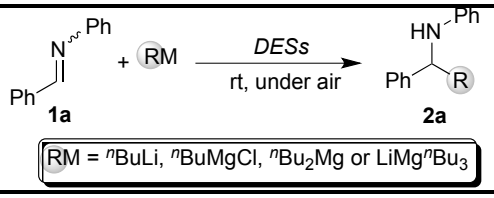
Table 1. Study of the addition reaction of organometallic reagents (RM = ^{n}BuLi, ^{n}BuMgCl, ^{n}Bu$_2$Mg and LiMg^{n}Bu$_3$) to *N*-Benzylideneaniline (**1a**) in different *Deep Eutectic Solvents*.[a,b]

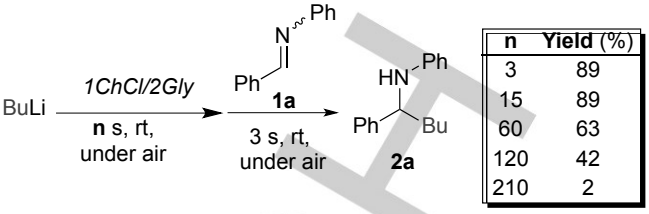


Entry	RM[b]	[mmol][b]	Solvent	Yield [%][c]
1	^{n}BuLi	1.3	1*ChCl*/2*Gly*	91
2	^{n}BuLi	1.4	1*ChCl*/2*Gly*	95
3	^{n}BuLi	1.8	1*ChCl*/2*Gly*	97
4	^{n}BuLi	2	1*ChCl*/2*Gly*	98
5	^{n}BuLi	1.4	1*ChCl*/2*EG*	66
6	^{n}BuLi	1.4	1*ChCl*/2H$_2$O	54
7	^{n}BuLi	1.4	H$_2$O	22
8	^{n}BuLi	1.4	Gly	38
9	^{n}BuMgCl	1.4	1*ChCl*/2*Gly*	1
10[d]	^{n}BuMgCl	1.4	1*ChCl*/2*Gly*	8
11	^{n}Bu$_2$Mg	1.4	1*ChCl*/2*Gly*	36
12	LiMg^{n}Bu$_3$	1.4	1*ChCl*/2*Gly*	72

[a] Reactions were performed under air, at room temperature and using 1 g of *DES*. Reaction time 3 s. 1 mmol of the imine **1a** was always used. [b] Commercial solutions of ^{n}BuLi (1.6 M in hexanes), ^{n}BuMgCl (1.0 M in THF) or dibutylmagnesium (1.0 M in hexanes) were used. LiMg^{n}Bu$_3$ was prepared in situ by mixing equimolar amounts of ^{n}BuLi and ^{n}Bu$_2$Mg in hexane. [c] Determined via ^{1}H NMR data using dibromomethane as internal standard. [d] ZnCl$_2$ (10 mol%) was added to the reaction mixture.

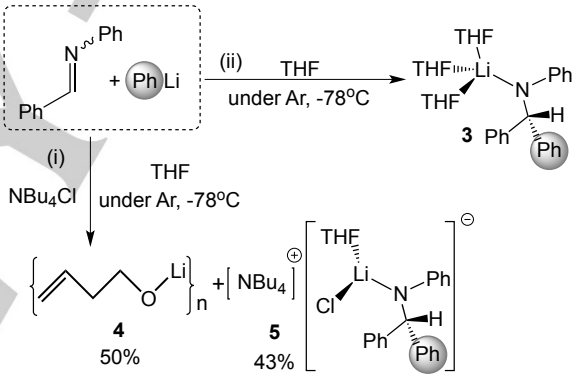
Next we assessed the effect of different *ChCl*-based *DESs* on this 1,2-addition reaction. Interestingly, replacing *Gly* for HBDs ethylene glycol (*EG*, entry 5) and water (entry 6) lowers the yield of amine **2a** (to 66 and 54% respectively). Notwithstanding, although the addition process is less efficient, its excellent chemoselectivity is maintained, without forming by-products, as only unreacted imine **1a** and amine **2a** were seen in the reaction crudes (see SI).[13] Contrastingly, when using HBDs containing carbonyl functionalities [such as urea or lactic acid], complex mixtures of products were observed from adding ^{n}BuLi across the C=O bond of these H-donor molecules, along with traces of **2a**.[14] Crucially, the use of inert-atmosphere Schlenk techniques or low temperature (0 to -78 ºC), mandatory when these additions are carried out in ethereal solvents, are not required using *DESs* (these solvent mixtures have a high heat capacity, so low temperatures are not needed to cool reactions).[15] The propensity of the *DES* mixture to favour ^{n}BuLi addition to **1a** over its competing hydrolysis is illustrated in entries 7 and 8 of Table 1, whereas using neat H$_2$O or *Gly*, in the absence of ammonium salt *ChCl*, furnishes **2a** in lower 22 and 38% yields respectively.

Highlighting the exciting potential of these green solvents, when the addition order of the reagents is reversed and ^{n}BuLi is introduced firstly to the eutectic mixture, which is stirred for 15 seconds under air before adding imine **1a**, product **2a** is obtained in a remarkably high 89% yield. Astonishingly, even if a one-minute interval is left between these reagents, the yield of **2a** is still good at 63%, emphasising the kinetic stability of ^{n}BuLi in this green solvent. Indeed, it is only after 3.5 minutes when the formation of **2a** is almost totally suppressed (Scheme 1).



Scheme 1 Assessing the time-dependent formation of **2a** when the order of addition of reagents is reversed

The reactivity of **1a** with other polar organometallics under the optimized reaction conditions was also investigated. ^{n}BuMgCl failed to produce **2a**, even when ZnCl$_2$ was employed as an additive (entries 9-10). Using ^{n}Bu$_2$Mg, which has recently shown promise for addition to bis(aryl)methylimines in toluene,[16] yields **2a** in a modest 36% yield (entry 11). Even anionically activated lithium magnesiate LiMg^{n}Bu$_3$ showed reduced reactivity (72%, entry 12), suggesting that under these conditions, the high polarity of Li-C bonds in RLi reagents is crucial for success of the 1,2-addition process.

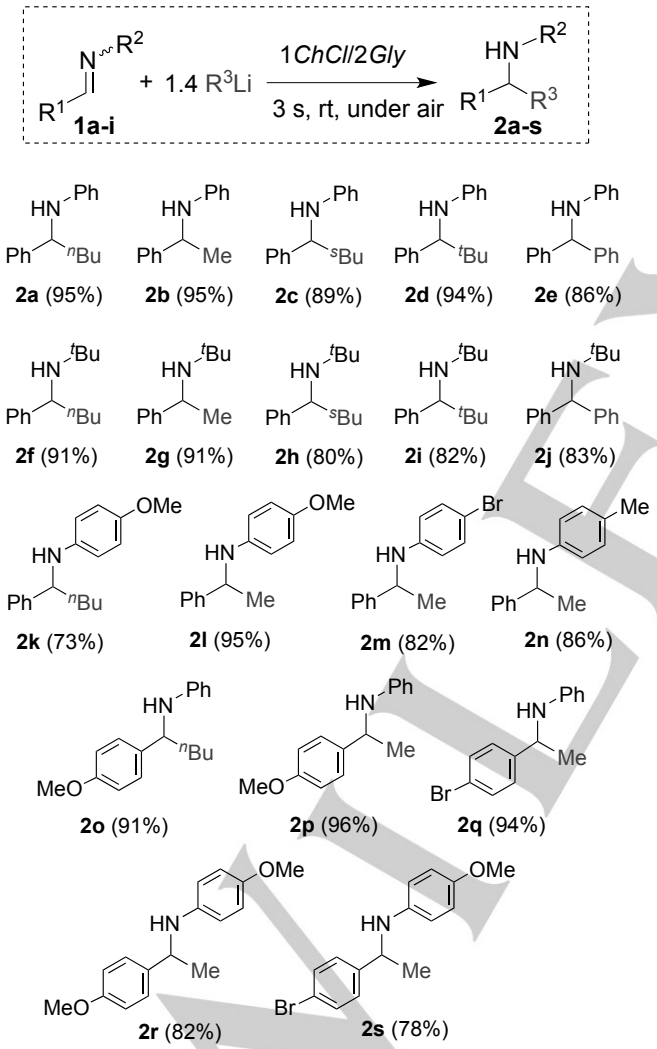


Scheme 2. Deleterious effect of ammonium salt on addition reaction between imine **1a** and phenyllithium.

Our previous work related the enhanced reactivity of polar organometallics in *DESs* with studies on the addition of RMgX reagents to ketones in organic solvents, where chemoselectivity can be enhanced by adding substoichiometric amounts of ammonium salt N^{n}Bu$_4$Cl.[8] We attributed this to forming kinetically activated mixed-ammonium magnesiate salts. Studies here reacting PhLi with **1a** in THF in the presence of N^{n}Bu$_4$Cl suggest the formation of related mixed ammonium lithiate species. However, in this case, these compounds appear to be extremely reactive in THF solutions, having a negative effect on addition chemoselectivity. Thus NMR monitoring of the reaction revealed the formation of lithium but-3-en-1 oxide **4**, resulting from α-deprotonation and subsequent ring-opening of THF (50% yield) along with ammonium lithiate complex **5** (Scheme 2 (i)), whose constitution was established by ^{1}H DOSY NMR experiments (see SI). Contrastingly, using PhLi the addition reaction occurs quantitatively to form amide [(THF)$_3$LiNPh(CHPh$_2$)] (**3**), whose structure was elucidated by X-ray crystallography (Scheme 2 (ii) and SI) This significant increase in the basicity of PhLi in THF on the addition of N^{n}Bu$_4$Cl contrasts with results observed using *DESs*, where no

substantial metallation of the glycerol (HBD component of the *DES*) is seen, hinting that though the formation of reactive ammonium lithiate species (via anionic activation by possible co-complexation with *ChCl*) can explain high efficiency of the addition reactions, other subtle effects such as the choice of HBD component or the nature of the ammonium salt employed should also play an important role in tuning the chemoselectivity of the reaction. Moreover, the different HBD abilities of water and alcohols cannot be disregarded, as recently shown by Capriati for "in water" RMgX mediated-additions to γ-chloroketones.[9c] Advancing the understanding of the interactions between the different components of *DESs* attracts widespread interest and debate,[11a] and to date only the structure of the *DES* reline (1*ChCl*/2Urea) has been elucidated using neutron diffraction.[17]

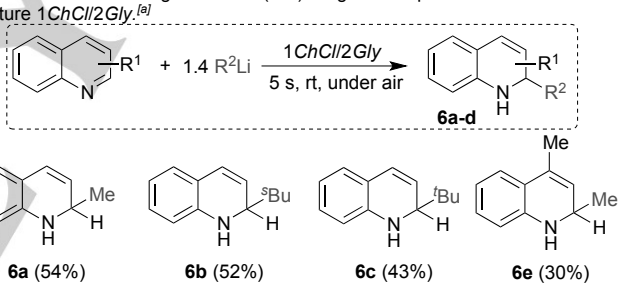
Table 2. Addition of organolithium (RLi) reagents to imines in the eutectic mixture 1*ChCl*/2*Gly*.[a]



[a] Reactions were run under air, at room temperature using 1 g of the eutectic mixture 1*ChCl*/2*Gly*. Reaction time 3 s. 1 mmol of imine was always used. Commercial solutions of ^{n}BuLi (1.6 M in hexanes), MeLi (1.6 M in diethyl ether), ^{s}BuLi (1.4 M in cyclohexane), ^{t}BuLi (1.9 M in pentane) and PhLi (1.8 M in dibutyl ether) were used. Yields were determined by ^{1}H NMR data using dibromomethane as internal standard.

Enthused by these findings we then ran the reaction using other RLi reagents and imines, to probe the scope of this transformation (see Table 2). For each substrate tested, the addition reaction in the eutectic mixture 1*ChCl*/2*Gly* was complete in a very short reaction time (3 s) and with high selectivity, as only unreacted imine and the desired amine (**2a-s**) were observed in the reaction crudes (see SI). Imine **1a** was chosen as the benchmark to study the addition of different organolithium reagents. Thus, under the previously optimized reaction conditions (1.4 equiv. of RLi, room temperature, under air, Table 1) both aliphatic (^{n}BuLi, MeLi, ^{s}BuLi, ^{t}BuLi) and aromatic (PhLi) organolithium reagents successfully add to imine **1a** yielding amines (**2a-e**) in excellent yields (86-95%). Results are particularly remarkable with sterically demanding ^{s}BuLi and ^{t}BuLi, which in general have a greater tendency to undergo β-hydride elimination, especially when employed at room temperature. But here, they chemoselectively produce amines (**2c-d** and **2h-i**, 80-94% yield), without need of a large excess of RLi (1.4 equiv.) or long reaction times (3 s). The method also offers an excellent substrate scope, showing similar amine conversions for *N*-aryl or *N*-alkyl substituted aldimines (Table 2). High chemoselectivity is also apparent as electron-withdrawing (Br; **2m**, **2q** and **2s**) and electron-donating substituents (MeO or Me; **2k**, **2l**, **2n**, **2o**, **2p** and **2r**) are tolerated on imine Ar groups, without observing possible competing processes such as Li-Br exchange (**2m**, **2q** and **2s**) or α-metallation.

Table 3. Addition of organolithium (RLi) reagents to quinolines in the eutectic mixture 1*ChCl*/2*Gly*.[a]



[a] Reactions were performed under air, at room temperature using 1 g of the eutectic mixture 1*ChCl*/2*Gly*. Reaction time 5 s. 1 mmol of quinoline was always employed. Commercial solutions of MeLi (1.6 M in diethyl ether), ^{s}BuLi (1.4 M in cyclohexane), and ^{t}BuLi (1.9 M in pentane) were used. Yields were determined by ^{1}H NMR data using dibromomethane as internal standard.

Next we extended this greener and air-compatible protocol to the even more challenging addition of organolithium reagents to aza-aromatic heterocyclic compounds which takes place with concomitant dearomatization of the heterocycle. The synthesis of 2-substituted dihydroquinolines, through adding RLi reagents to quinoline, is a commonly used methodology for the production of tetrahydroquinoline-containing alkaloids.[18] Using conventional methods limited by low temperatures, an inert atmosphere and scrupulously dry solvents, these reactions usually yield mixtures of re-aromatized 2-substituted quinoline and C2- and C4 dihydroquinolines.[19] In contrast, we found that under the same optimized reaction conditions (*1ChCl*/2*Gly* as solvent, at room temperature in air, 1.4 eq RLi in Table 3) aliphatic (MeLi, ^{s}BuLi, ^{t}BuLi) organolithium reagents add instantaneously (5 s) to quinoline to furnish exclusively C2-substituted dihydroquinolines **6a-d**. Although reaction yields are moderate (30-54%), chemoselectivities are remarkable, as no by-products were seen in reaction crudes, only unreacted quinoline and target 2-substituted dihydroquinolines (see SI).

In summary, this work has shown that replacing conventional toxic ethereal solvents by green, biorenewable Deep Eutectic Solvents facilitates the successful chemoselective addition of organolithium reagents to imines and quinolines under standard bench experimental conditions (room temperature and under air), thus edging closer towards reaching aerobic/hydrous polar organometallic chemistry and at the same time advancing Main-Group based Green Chemistry.

Experimental Section

Full experimental details and copies of NMR spectra are included in the Supporting Information. CCDC 1503241 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

Acknowledgements

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Keywords: Organolithium reagents • Deep Eutectic Solvents • Green Chemistry • salt activation • Imines •

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Layout 1:

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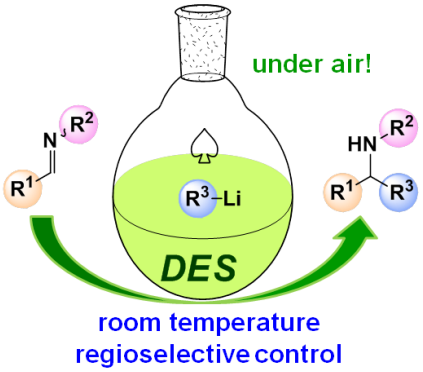
The Green(air), the better!

Moving closer to the dream of hydrous/aerobic organolithium chemistry, replacing toxic organic solvents by green and biorenewable *Deep Eutectic Solvents* (*DESs*) enables regioselective addition of organolithium reagents to non-activated imines at room temperature in air.



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Supporting Information

Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions

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Table of Contents

General Methods. All reagents were obtained from commercial suppliers and used without further purification with the exception of the *Deep Eutectic Solvents*[1] and imines **1c-i**[2] which were prepared by following the methods reported in the literature. Organolithium reagents were obtained from commercial suppliers: (i) *n*-butyl lithium (1.6 M solution in hexane); (ii) methyl lithium (1.6 M solution in diethyl ether); (iii) *sec*-butyl lithium (1.4 M solution in cyclohexane); (iv) *tert*-butyl lithium (1.9 M solution in pentane) and (v) phenyl lithium (1.8 M in dibutyl ether). The concentration of these solutions was established by titration with salicylaldehyde phenylhydrazone.[3] Solvent free PhLi was prepared as a solid and stored in the glove box, following the reported procedure.[4] NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, operating at 400.13 MHz for ^{1}H, 150.32 MHz for ^{7}Li and 100.62 MHz for ^{13}C. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser.

General procedure for addition reactions of RLi reagents with imines in *DESs*.
Syntheses were performed under air and at room temperature. In a glass tube, the appropriate imine (**1a-1i**, 1 mmol) was dissolved in the corresponding *Deep Eutectic Solvent* (*DES*, 1 g) under air, followed by the addition of the organolithium reagent (RLi, 1.4 mmol) at room temperature, and the reaction mixture was stirred for 3 seconds. The reaction is stopped by addition of a saturated solution of the Rochelle salt (sodium potassium tartrate tetrahydrate) and the organic products were extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. Yields of the reaction crudes were determined by ^{1}H NMR methodology using dibromomethane (1 mmol, 70.8 μL) as internal standard. Amines **2a-s** are known compounds and their ^{1}H NMR spectroscopic data matched with that reported in the literature.[2,5]

X-ray crystallography. Data for sample **3**, were measured with an Oxford Diffraction diffractometer[6] with monochromated Mo Kα (λ= 0.71073 Å) radiation. Refinement was to convergence on F^2 and against all independent reflections by the full-matrix least squares method using the SHELXL program.[7] Selected crystallographic and refinement details are given in Table ESI-1. CCDC 1503241 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

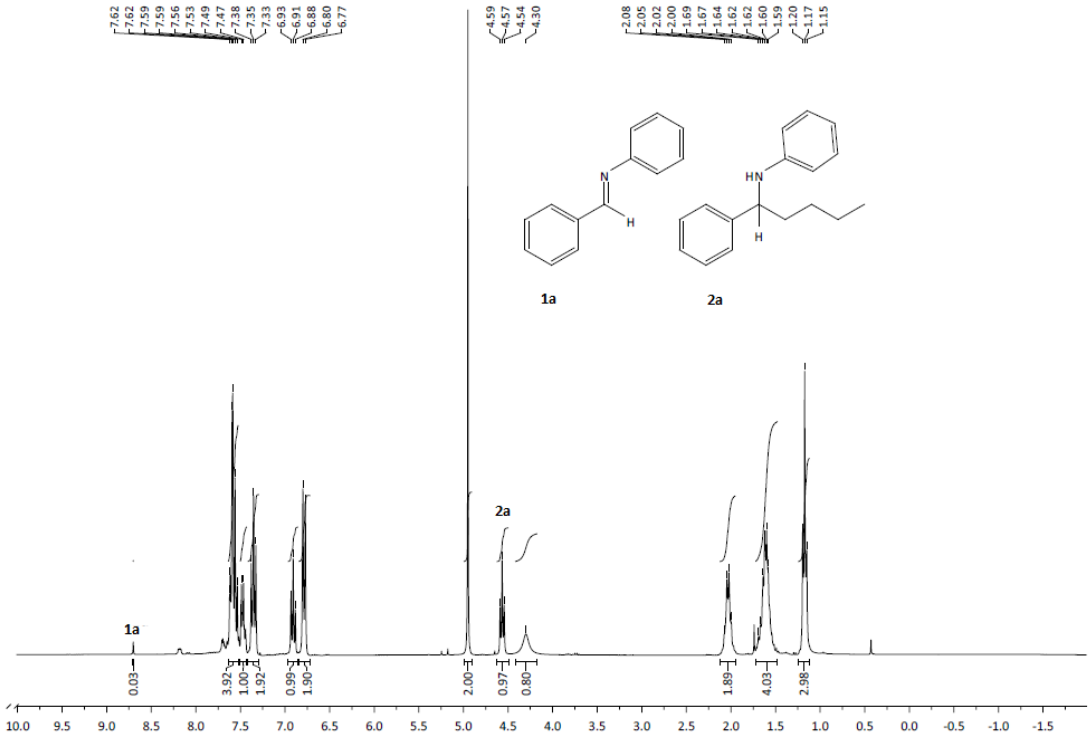

Figure ESI-1. ^{1}H NMR spectrum of the reaction crude from the addition of ^{n}BuLi to *N*-benzylideneaniline (**1a**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

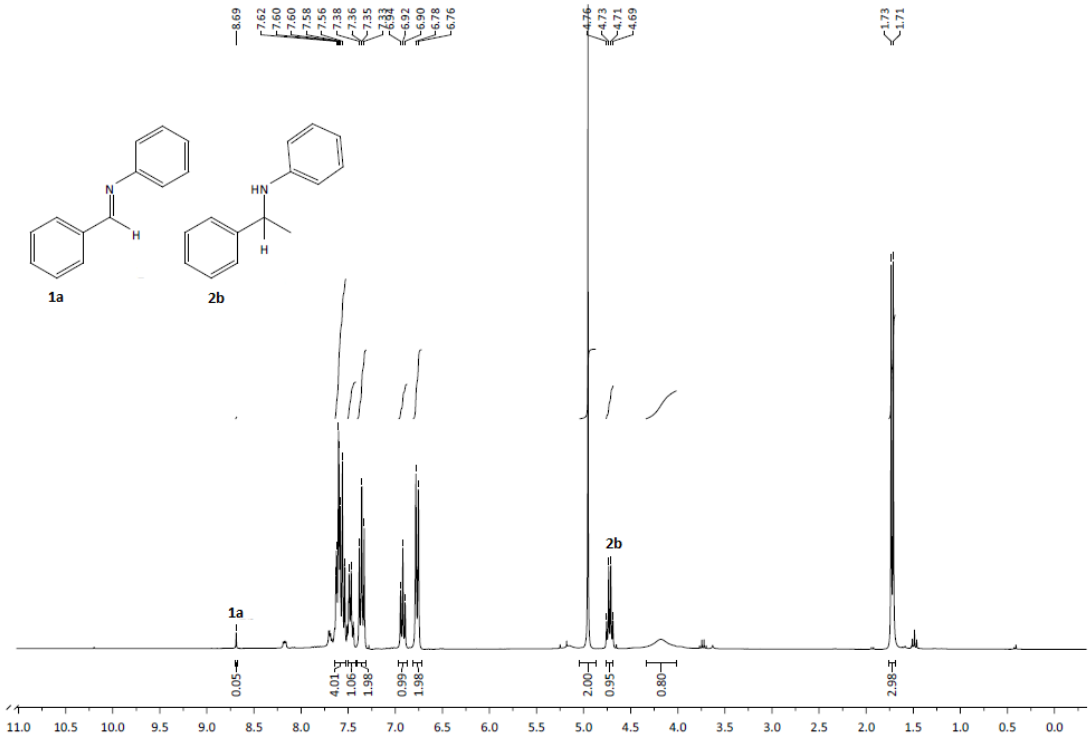

Figure ESI-2. ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-benzylideneaniline (**1a**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

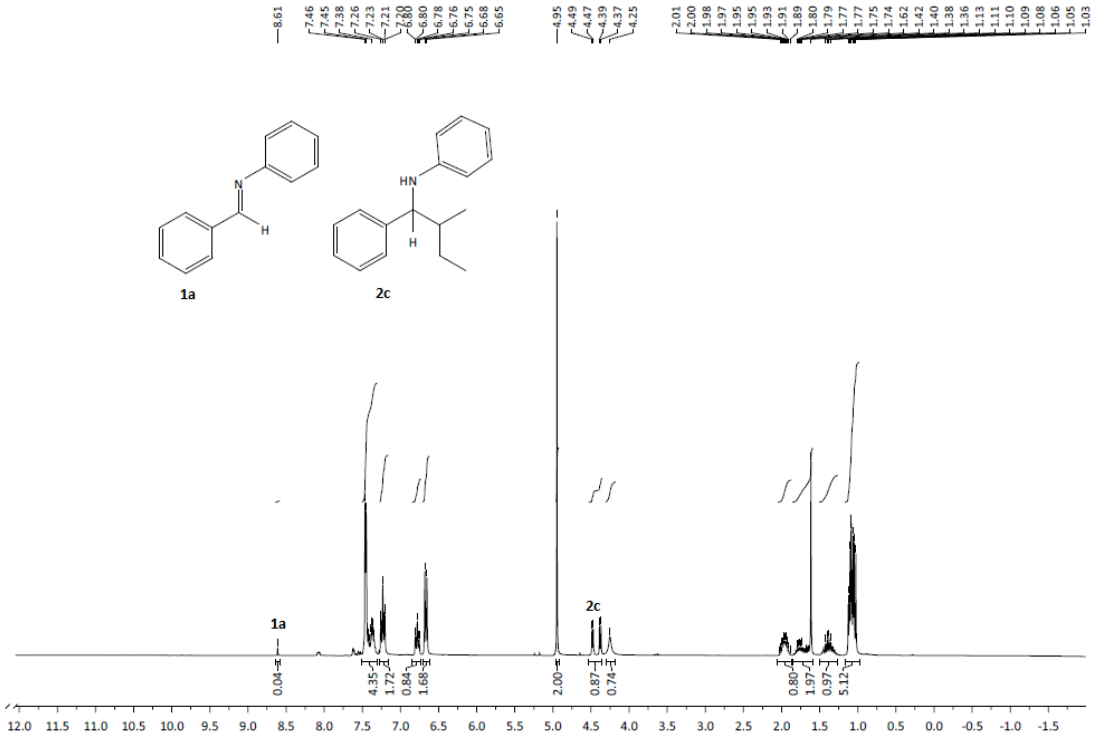

Figure ESI-3. ^{1}H NMR spectrum of the reaction crude from the addition of ^{s}BuLi to *N*-benzylideneaniline (**1a**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

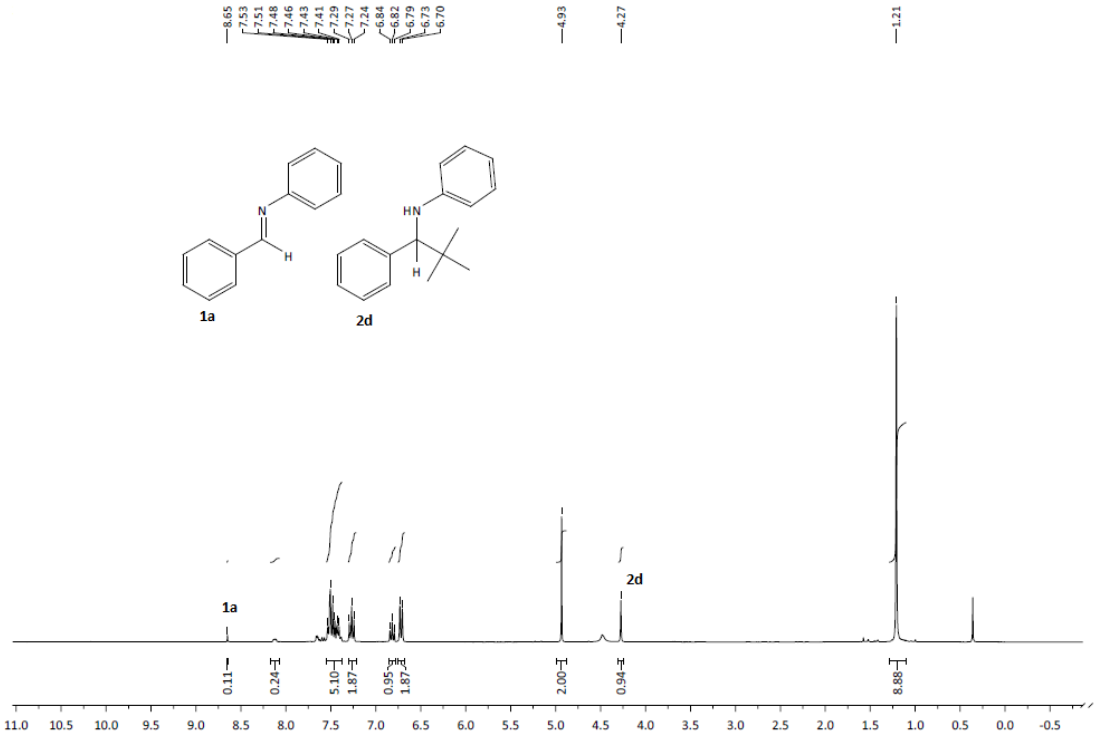

Figure ESI-4. ^{1}H NMR spectrum of the reaction crude from the addition of ^{t}BuLi to *N*-benzylideneaniline (**1a**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

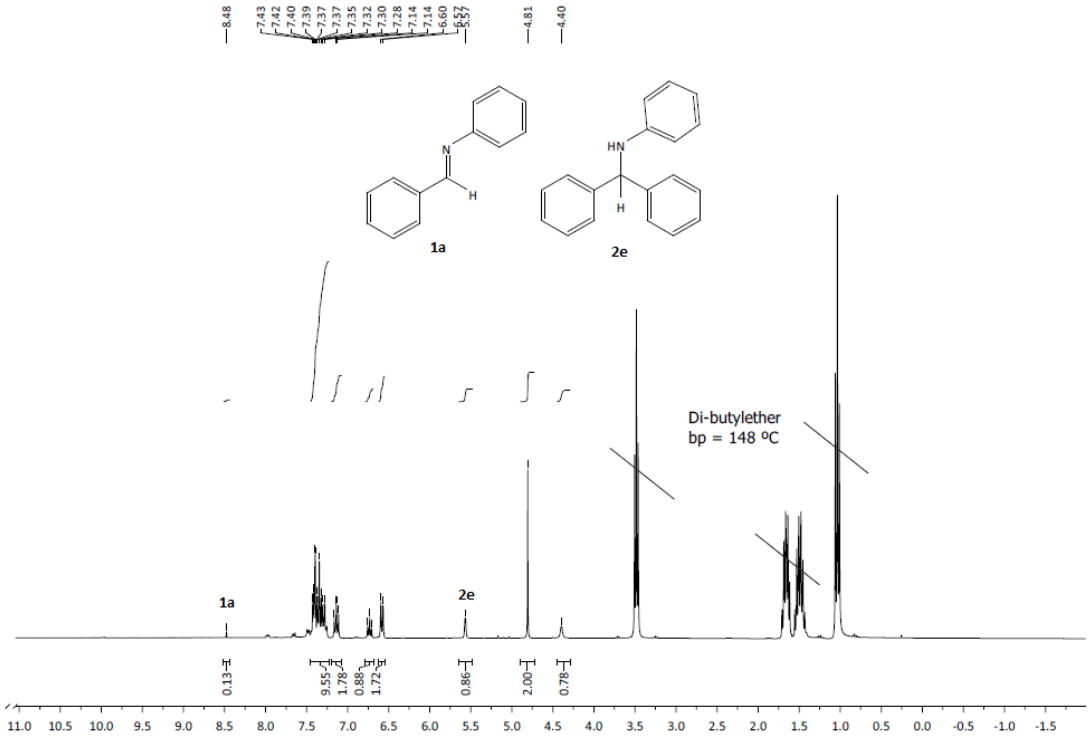

Figure ESI-5. ^{1}H NMR spectrum of the reaction crude from the addition of PhLi to *N*-benzylideneaniline (**1a**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

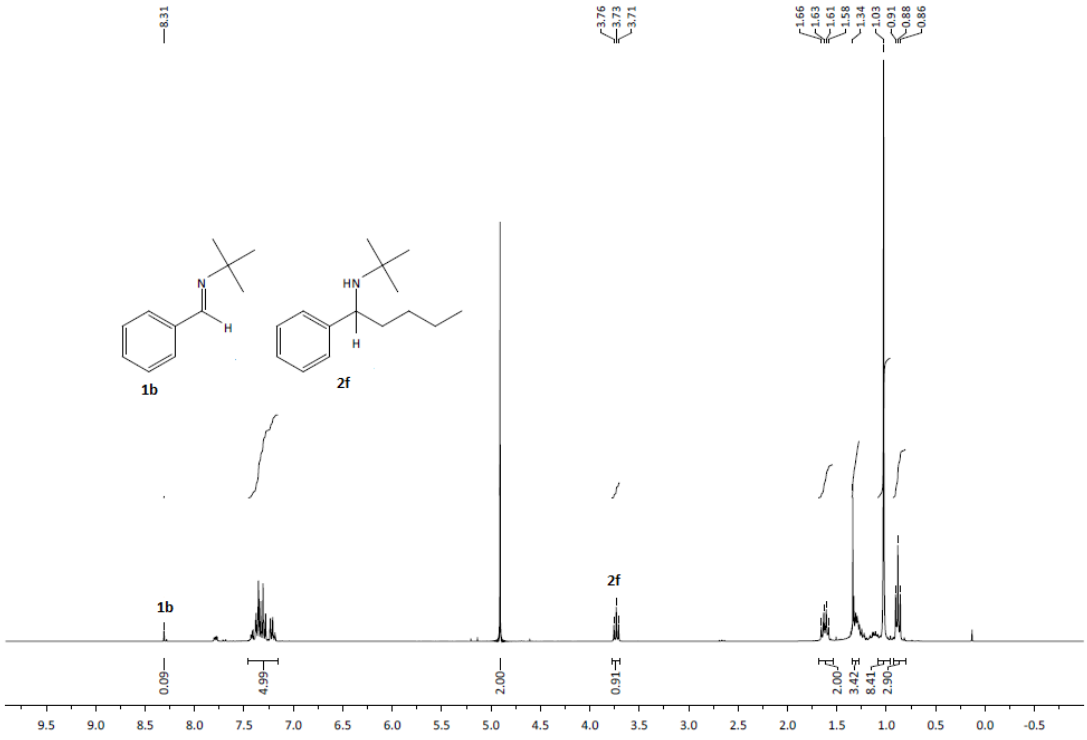

Figure ESI-6 ^{1}H NMR spectrum of the reaction crude from the addition of ^{n}BuLi to *N*-benzylidene-*ter*t-butylamine (**1b**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

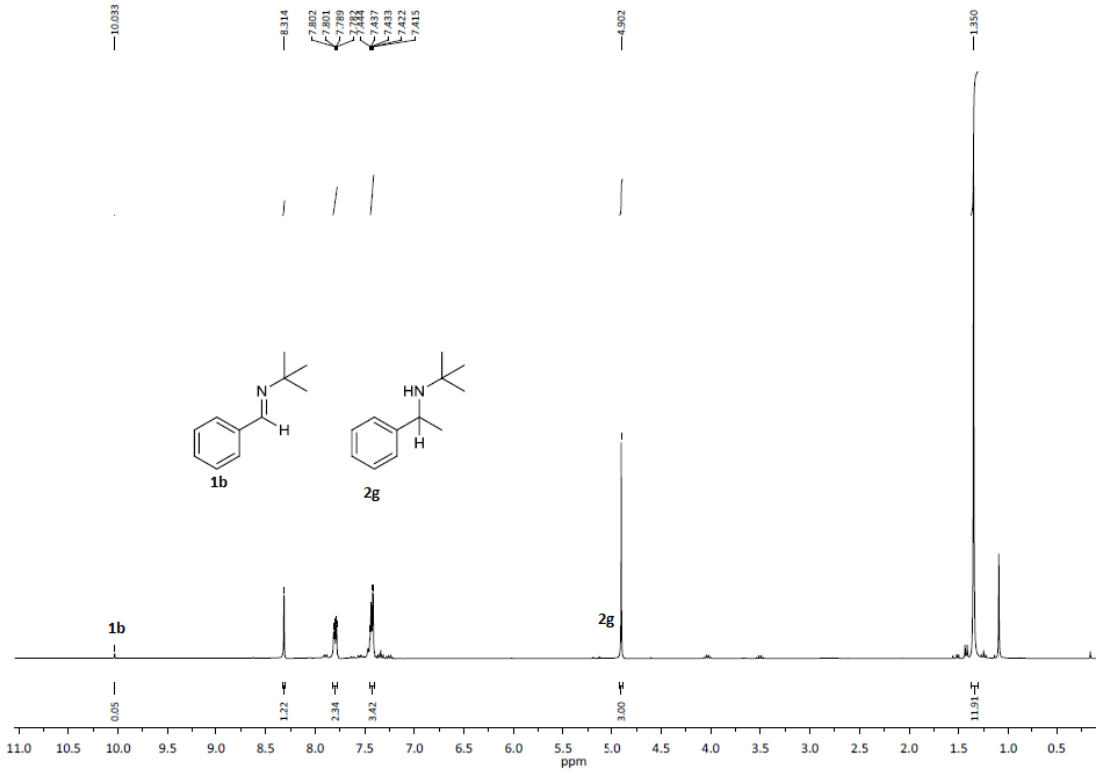

Figure ESI-7 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-benzylidene-*tert*-butylamine (**1b**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

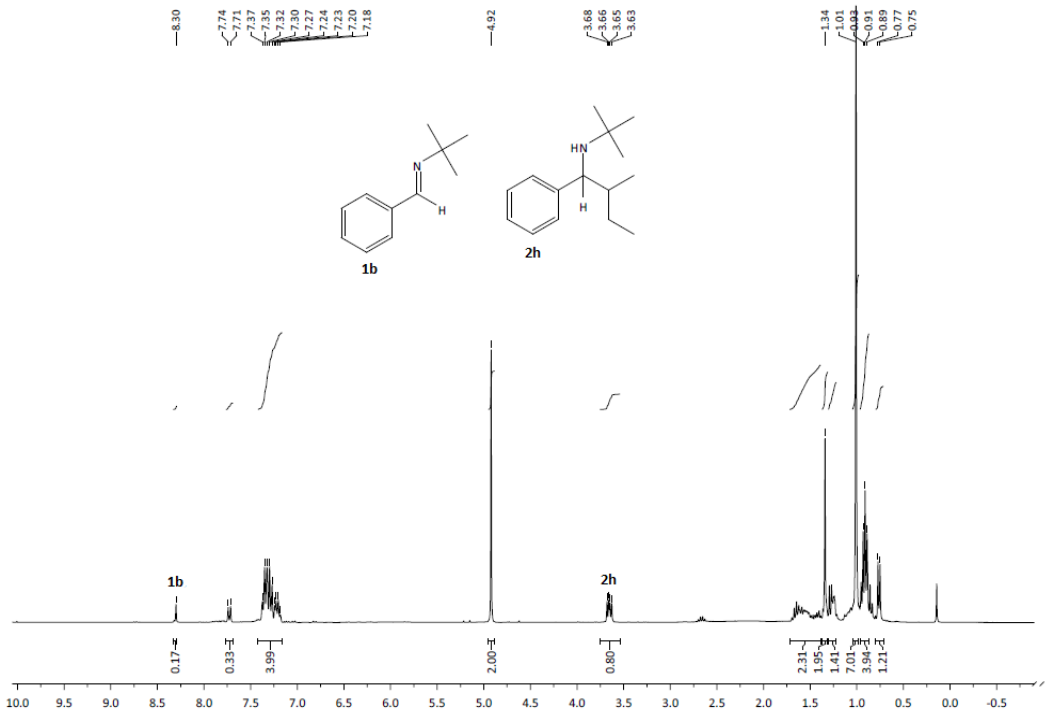

Figure ESI-8 ^{1}H NMR spectrum of the reaction crude from the addition of ^{s}BuLi to *N*-benzylidene-*tert*-butylamine (**1b**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

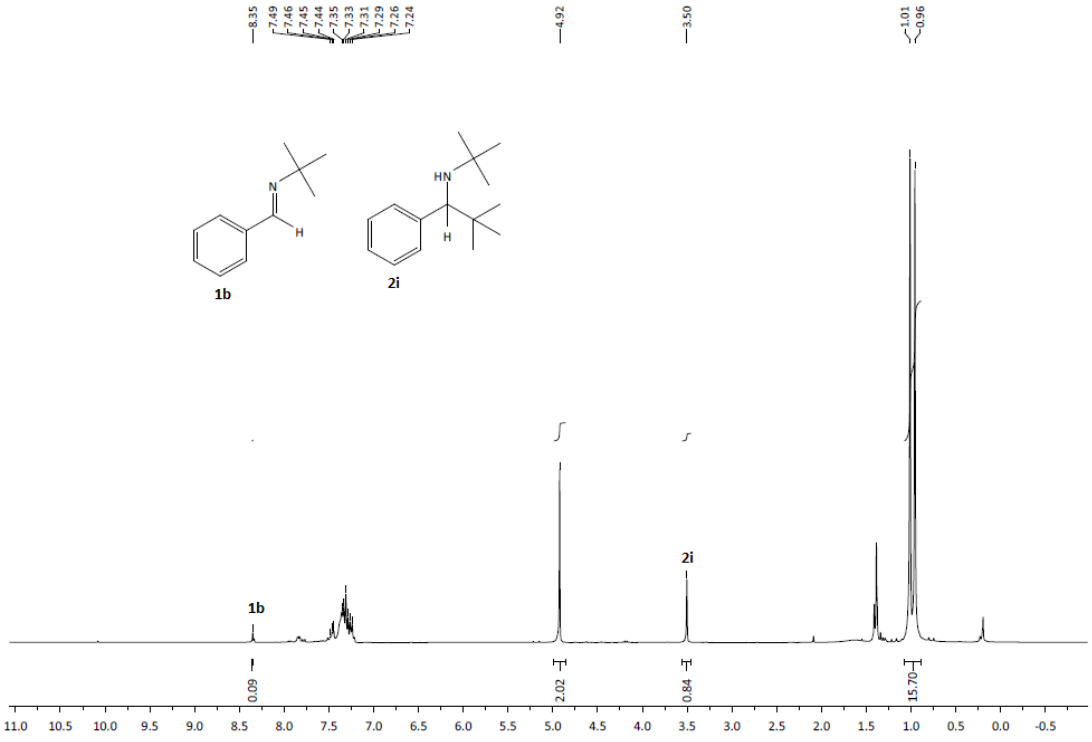

Figure ESI-9 ^{1}H NMR spectrum of the reaction crude from the addition of ^{t}BuLi to *N*-benzylidene-*tert*-butylamine (**1b**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

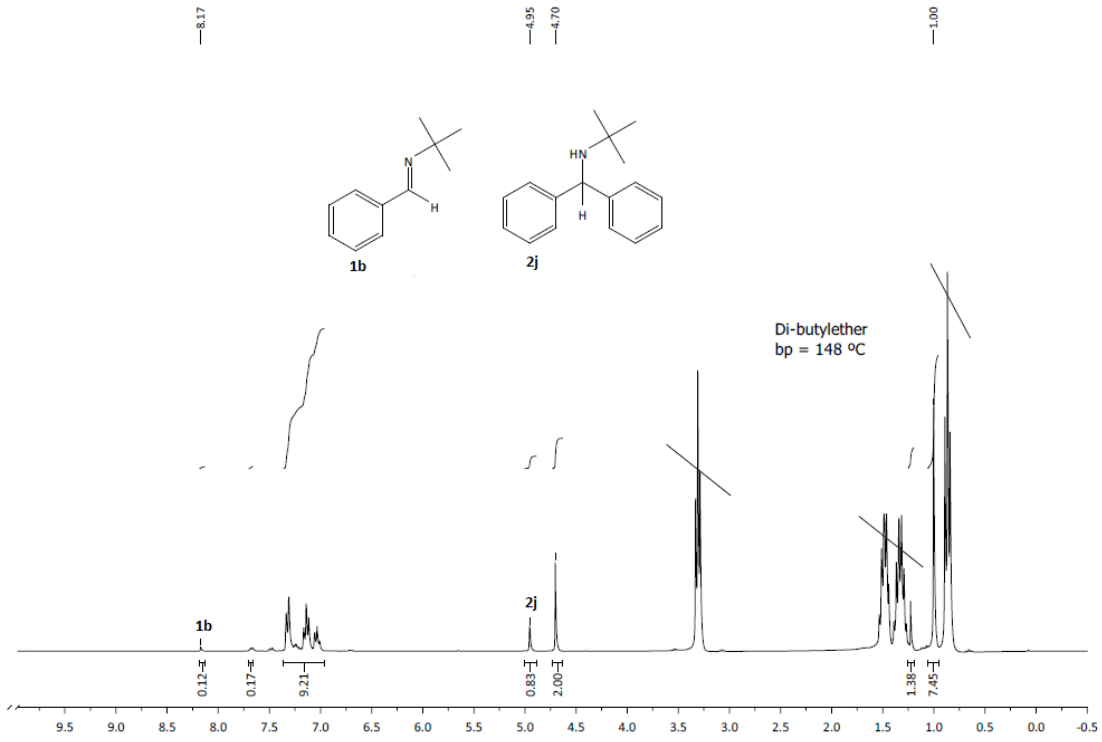

Figure ESI-10 ^{1}H NMR spectrum of the reaction crude from the addition of PhLi to *N*-benzylidene-*tert*-butylamine (**1b**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

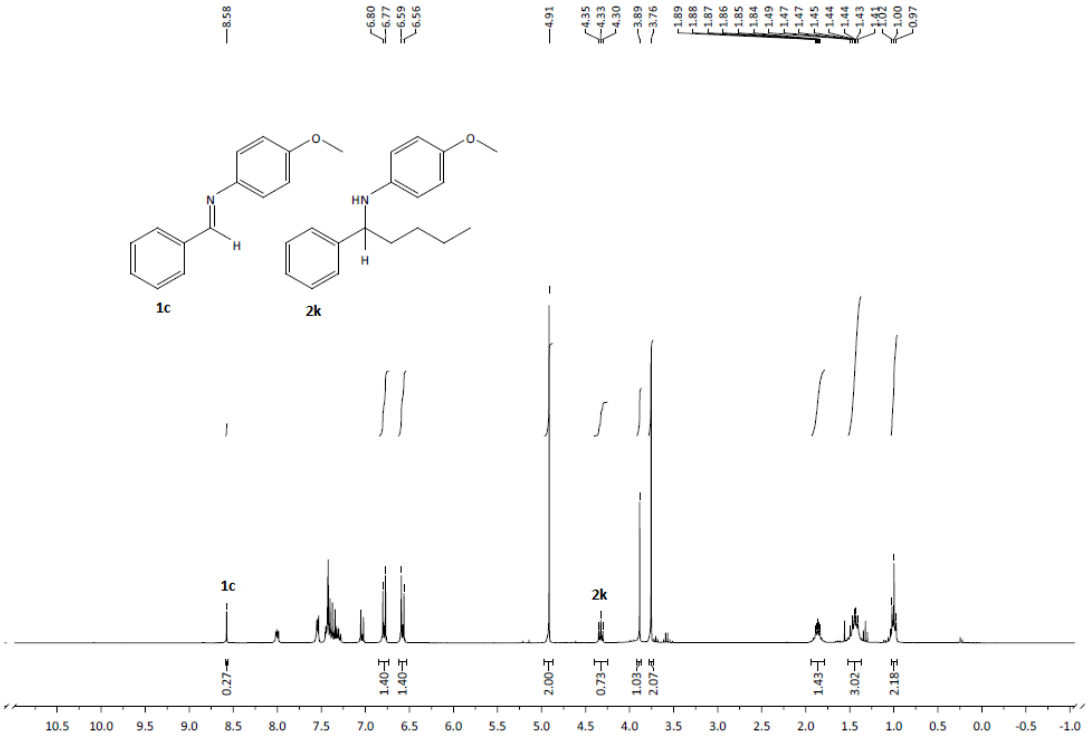

Figure ESI-11 ^{1}H NMR spectrum of the reaction crude from the addition of ^{n}BuLi to *N*-benzylidene-4-methoxyaniline (**1c**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

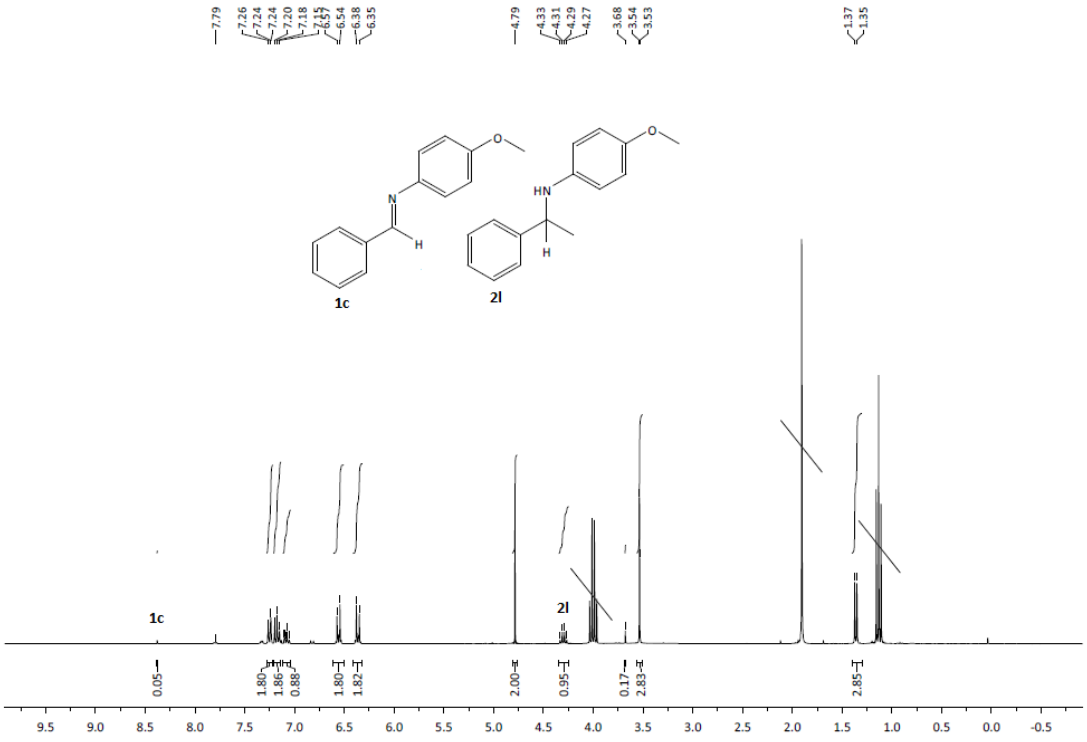

Figure ESI-12 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-benzylidene-4-methoxyaniline (**1c**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

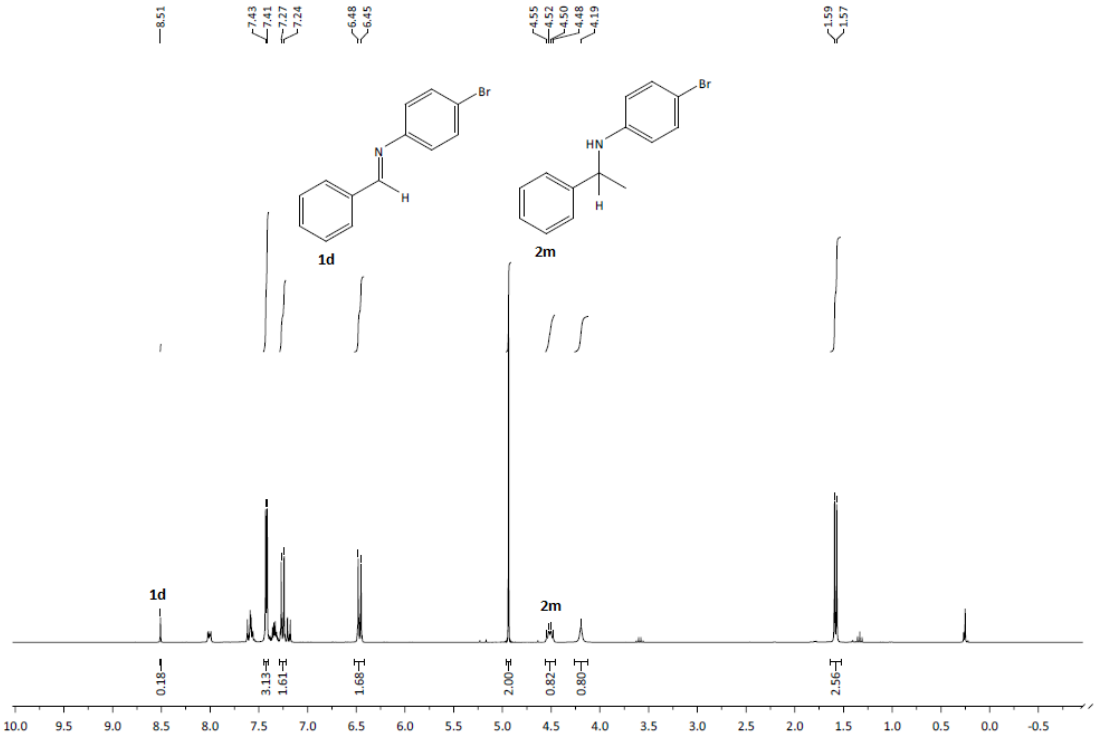

Figure ESI-13 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-benzylidene-4-bromoaniline (**1d**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

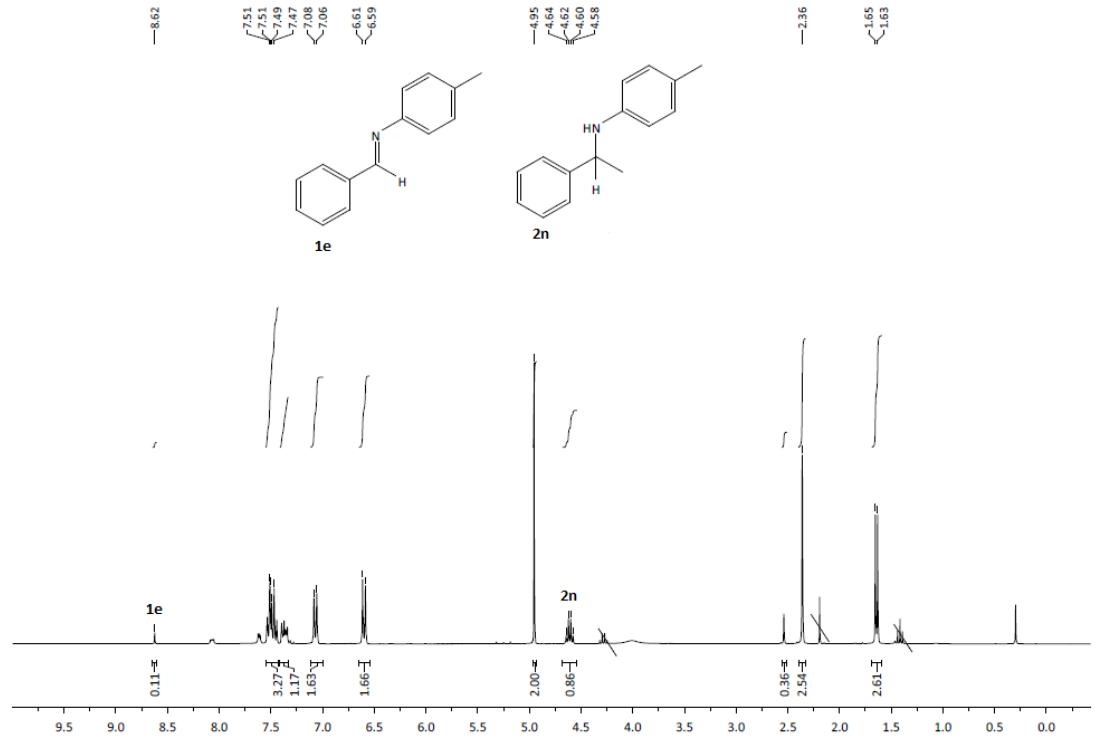

Figure ESI-14 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-benzylidene-4-methylaniline (**1e**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

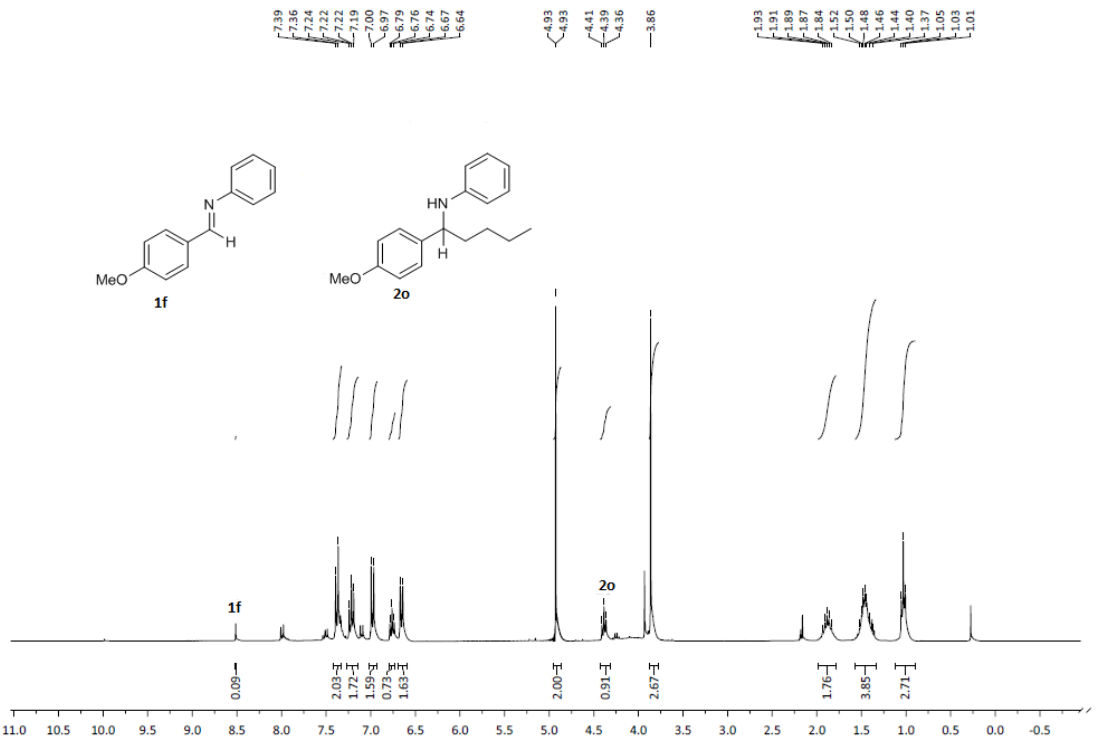

Figure ESI-15 ^{1}H NMR spectrum of the reaction crude from the addition of ^{n}BuLi to *N*-(4-methoxybenzylidene)aniline (**1f**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

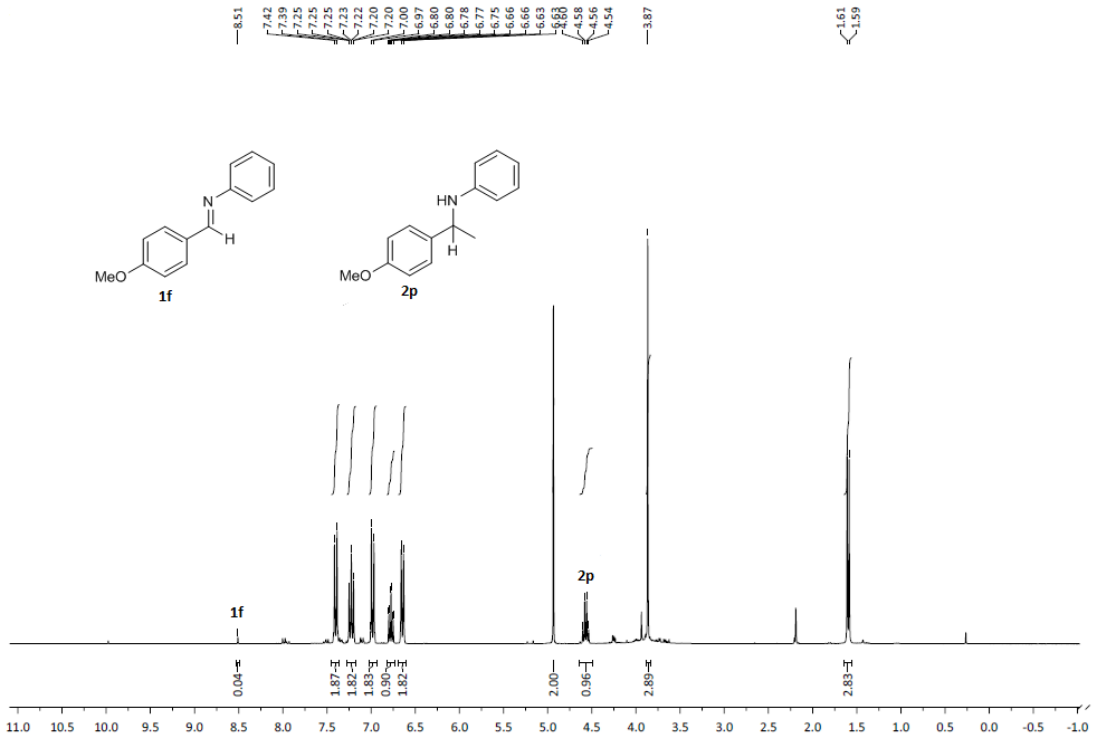

Figure ESI-16 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-(4-methoxybenzylidene)aniline (**1f**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

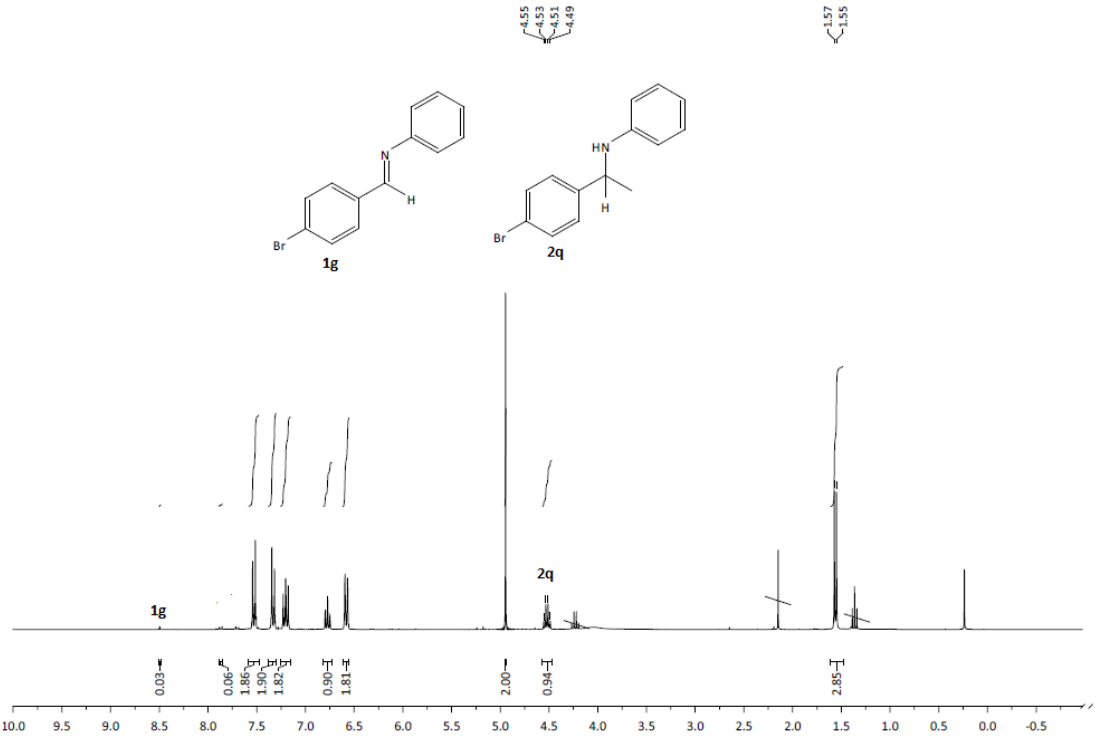

Figure ESI-17 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-(4-bromobenzylidene)aniline (**1g**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

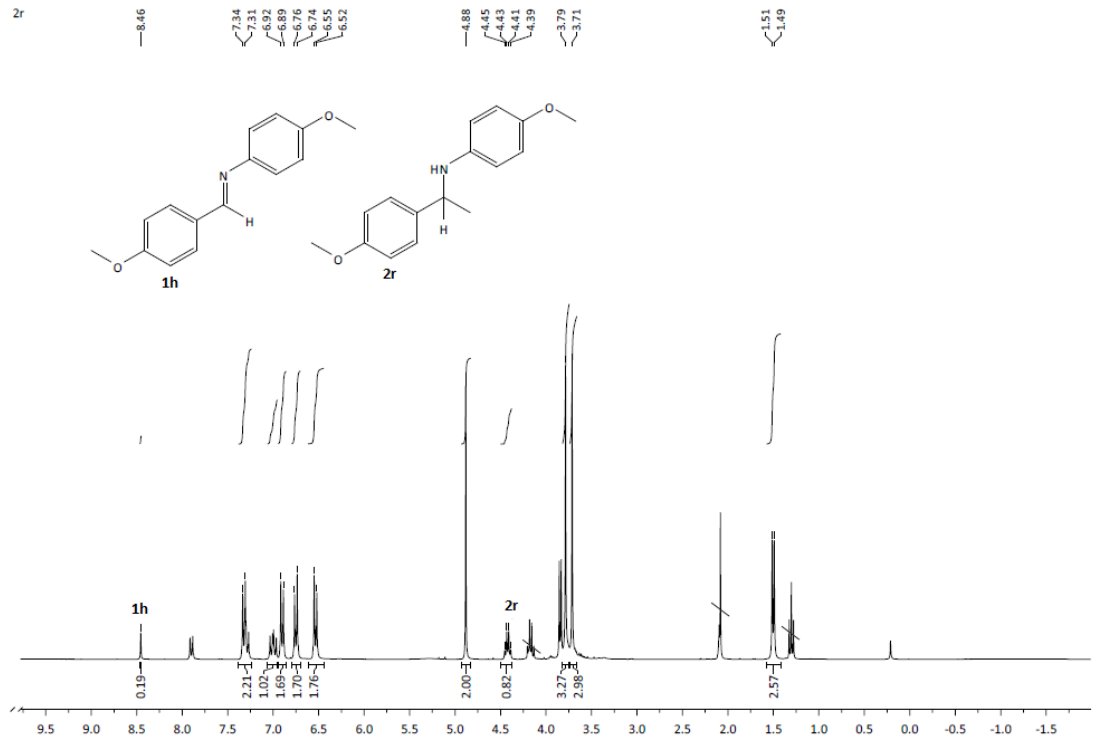

Figure ESI-18 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to 4-methoxy-*N*-(4-methoxybenzylidene)aniline (**1h**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

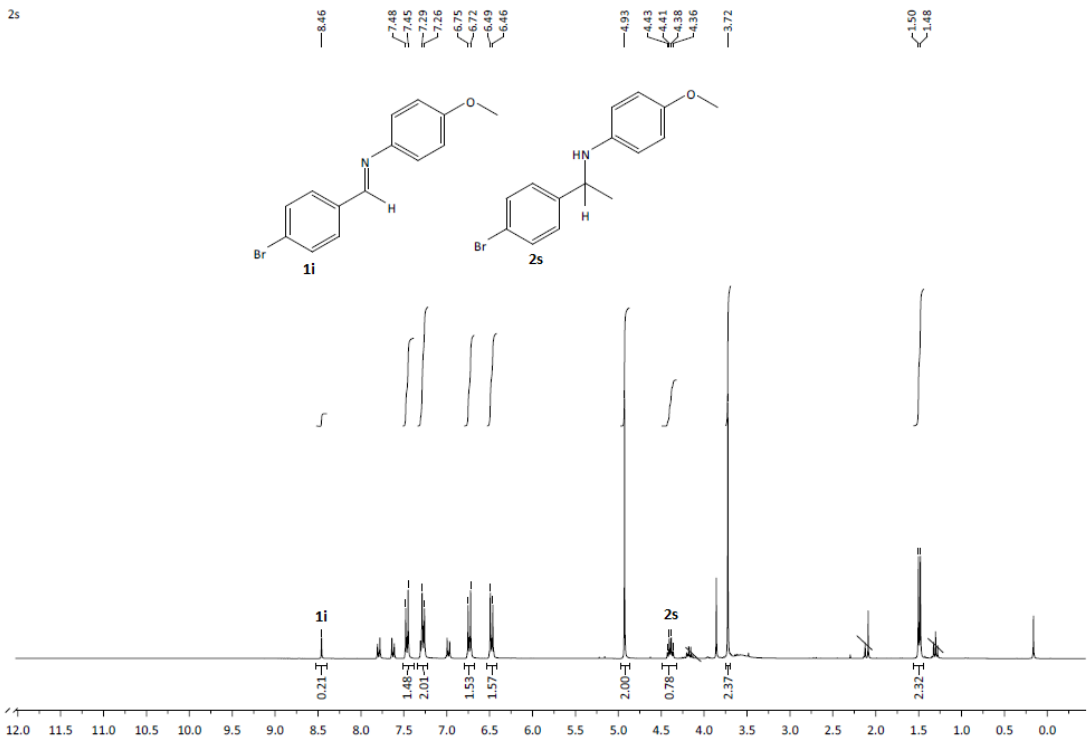

Figure ESI-19 ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to *N*-(4-bromobenzylidene)-4-methoxyaniline (**1i**) in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

General procedure for addition reactions of RLi reagents with quinolines in *DESs*. Syntheses were performed under air and at room temperature. In a glass tube, the appropriate quinoline (1 mmol) was dissolved in the corresponding *Deep Eutectic Solvent* (*DES*, 1 g) under air, followed by the addition of the organolithium reagent (RLi, 1.4 mmol) at room temperature, and the reaction mixture was stirred for 5 seconds. Addition of saturated solution of Rochelle salt to the reaction crude allows the straightforward separation of the desired organic product, as described for amines **2a-s**. Yields were determined by ^{1}H NMR methodology using dibromomethane as internal standard. C2-substituted dihydroquinolines **6a-d** are known compounds and their ^{1}H NMR data matched with that reported in the literature.[8]

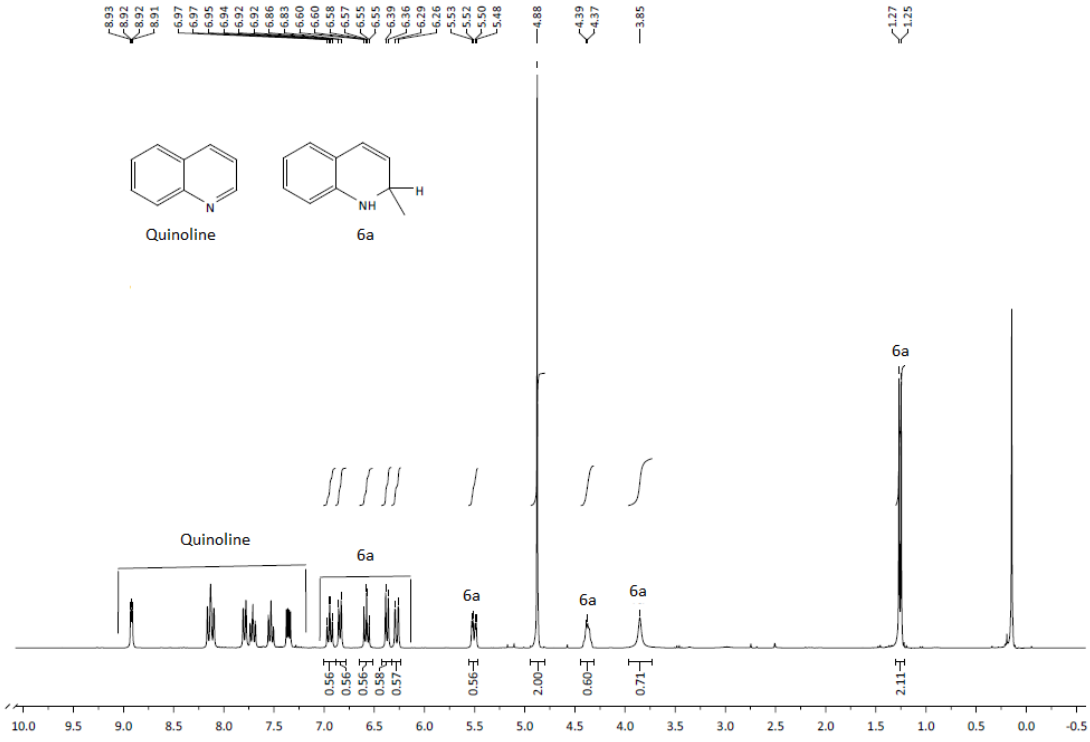

Figure ESI-20. ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to quinoline in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

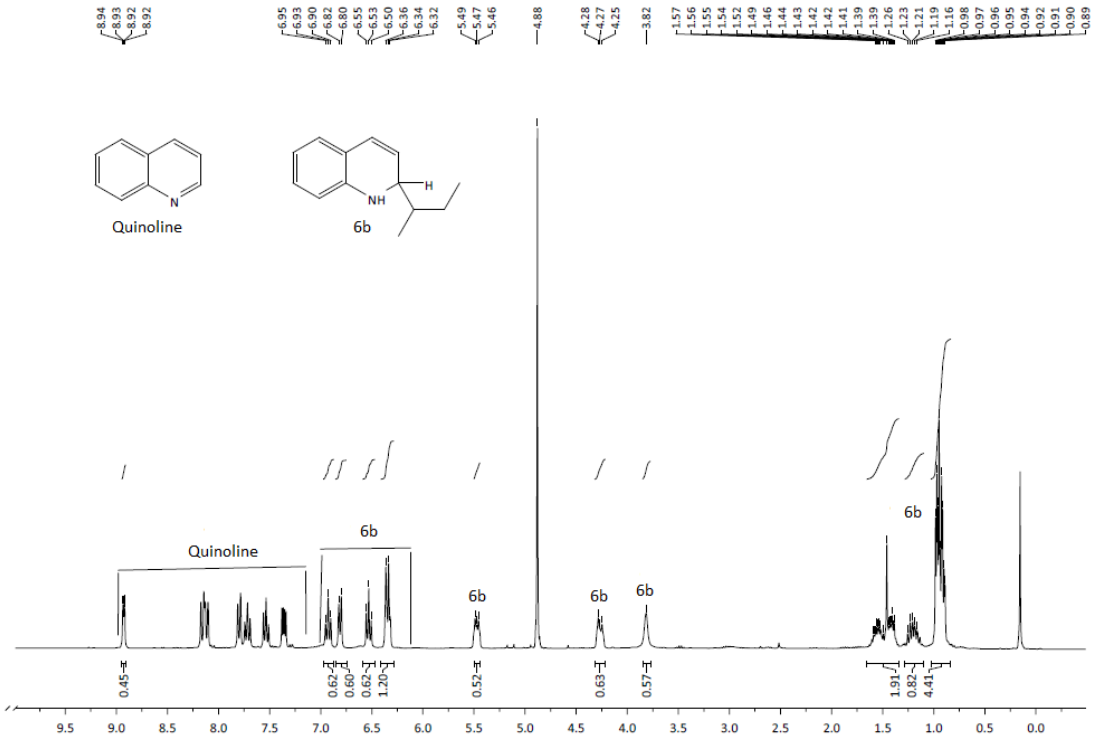

Figure ESI-21 ^{1}H NMR spectrum of the reaction crude from the addition of ^{s}BuLi to quinoline in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

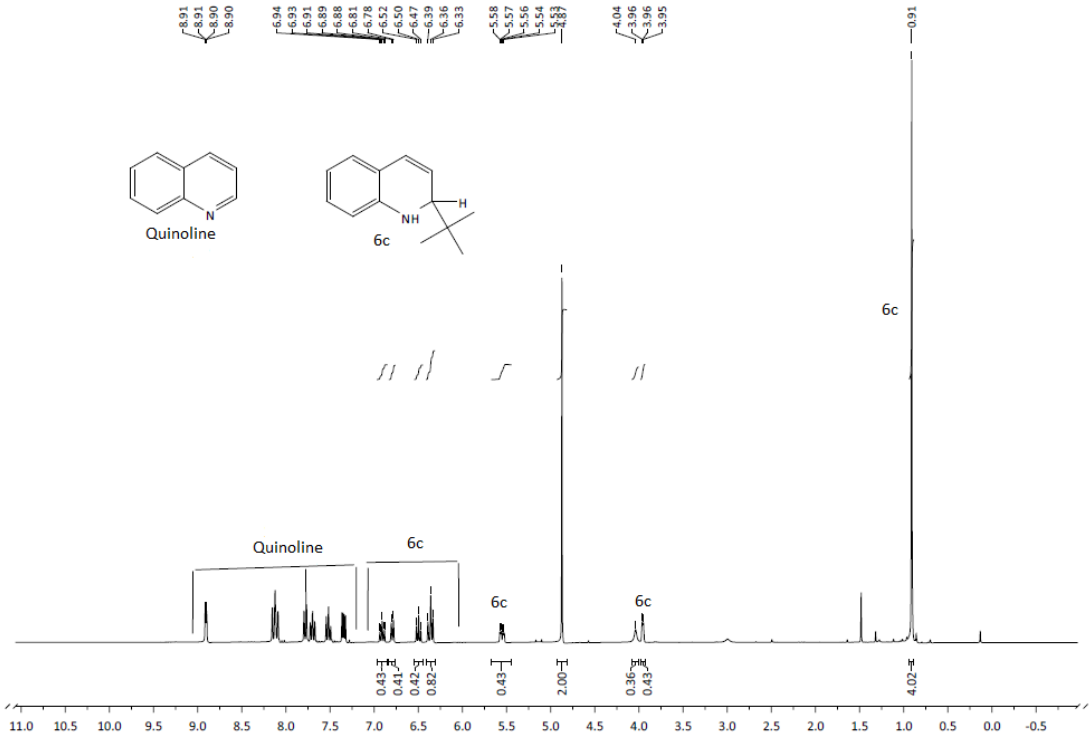

Figure ESI-22. ^{1}H NMR spectrum of the reaction crude from the addition of ^{t}BuLi to quinoline in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

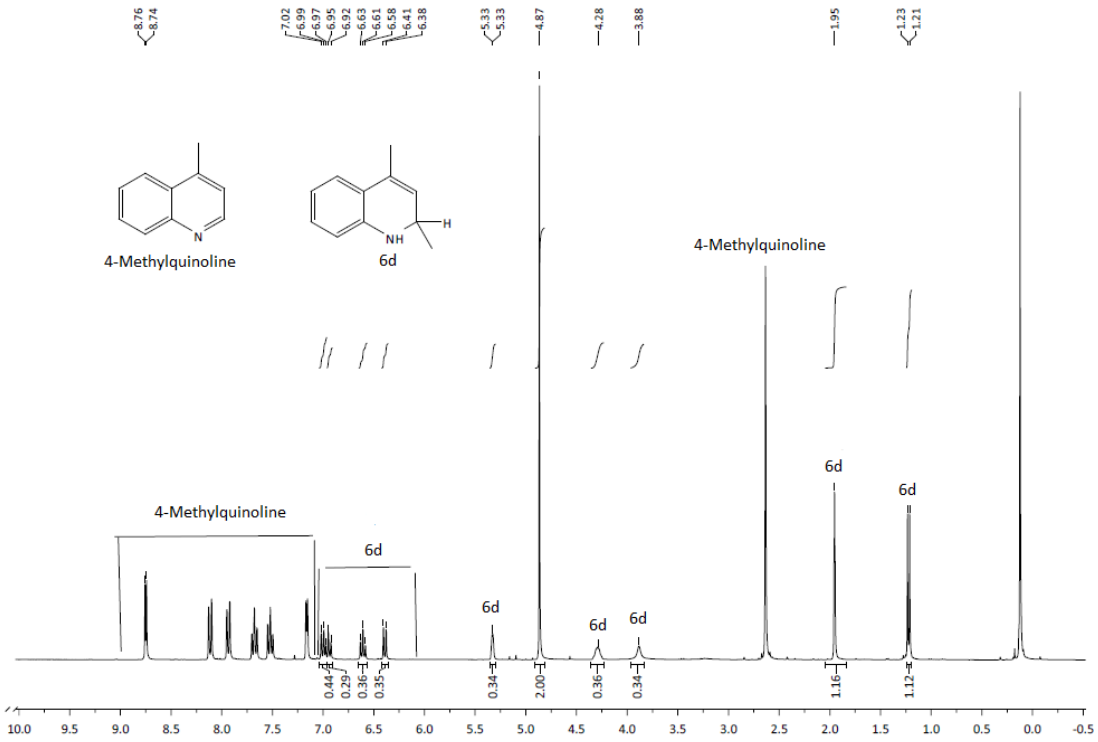

Figure ESI-23. ^{1}H NMR spectrum of the reaction crude from the addition of MeLi to 4-methylquinoline in 1*ChCl*/2*Gly*, using CH_2Br_2 (4.9 ppm) as internal standard in $CDCl_3$.

Synthesis and X-Ray Crystal Structure Determination of Compound 3

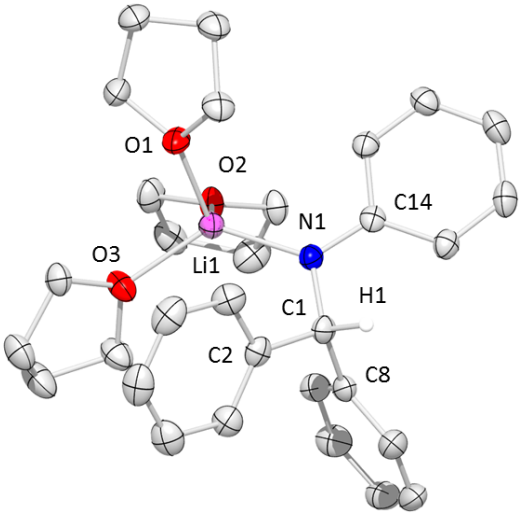

Figure ESI-24. Solid state structure of compound **3** with thermal ellipsoids at 50% of probability. Hydrogen atoms except that one attached to C1 are omitted for clarity. Selected bond distances (Å) and angles (◦) Li1-O1 1.969(2), Li1-O2 2.028(3), Li1-O3 1.988(3), Li1-N1 2.004(2), N1-C1 1.4569(17); O1-Li1-O2 111.56(12), O1-Li1-O3 100.90(11), O1-Li1-N1 111.82(12), O2-Li1-O3 93.89(10), O2-Li1-N1 109.93(11), O3-Li1-N1 127.22(13), C1-N1-C14 114.80(10), C1-N1-Li1 121.48(11), C14-N1-Li1 123.04(11).

Table ESI-1. Selected crystallographic and refinement parameters.

	3
Empirical formula	$C_{31}H_{40}LiNO_3$
Molecular Weight	481.58
Temperature (K)	123(2)
Wavelength (Å)	0.71073
Crystal system,	monoclinic
Space group	P 2_1/c
a (Å)	18.0621(5)
b (Å)	14.3719(5)
c (Å)	10.4884(3)
β (°)	97.603(3)
Cell volume (Å^3)	2698.71(14)
Z	4
ρ_{calc} (g.cm^{-3})	1.185
μ (mm^{-1})	0.074
2θ max(°)	58.95
Index ranges	-23≤*h*≤23 -15≤*k*≤19 -14≤*l*≤14
Reflections collected	16800
Reflections unique	6901
Reflections obs.	5113
R_{int}	0.0325
No. Parameters	325
Goodness-of-fit-on F^2 (*GOF*)	1.024
Final *R* indices [*I*>2σ(*I*)]	0.0524
R indices (all data)	0.1174
Largest diff. peak and hole (e Å^{-3})	0.244 and -0.197

Synthesis of [(THF)$_3$LiN(Ph)(CHPh$_2$)](3)

To a THF (10 mL) solution of *N*-benzylideneaniline **1a** (1 mmol, 0.181g), LiPh (1 mmol, 0.084g) was added. After 30 min stirring at room temperature the volume of the pale yellow solution was reduced under vacuum to 1 mL of THF. Then 2 mL of hexane was introduced, and the solution was stored at -30 °C overnight, affording colorless crystals of compound **3** (0.32 g, 66%). ^{1}H NMR (400 MHz, 298 K, d$_8$-THF) δ (ppm) = 1.77 (m, 4H, THF), 3.61 (m, 4H, THF), 5.25 (s, 1H, C*H*Ph$_2$), 5.73 (t, *J* = 7.2 Hz, 1H, *para*-C*H*, N*Ph*), 5.98 (broad d, 2H, *ortho*-C*H*, N*Ph*), 6.6 (t, *J* = 7.2 Hz, 2H, *meta*-C*H*, N*Ph*), 7.03 (t, *J* = 7.2 Hz, 2H, *para*-C*H*, CH*Ph$_2$*), 7.14 (t, *J* = 7.2 Hz, 4H, *meta*-C*H*, CH*Ph$_2$*), 7.28 (d, *J* = 7.2 Hz, 4H, *ortho*-C*H*, CH*Ph$_2$*). ^{13}C NMR (100 MHz, 298 K, C$_6$D$_6$) δ (ppm) = 26.1 (THF), 68.0 (THF), 68.2 (*C*HPh$_2$), 106.6 (*para*-*C*H, N*Ph*), 113.7 (broad, *ortho*-*C*H, N*Ph*), 125.6 (*para*-*C*H, CH*Ph$_2$*), 128.2 (*meta*-*C*H,

CH*Ph*$_2$), 128.7 (*meta*-*C*H, N*Ph*) 128.8 (*ortho*-*C*H, CH*Ph*$_2$), 150.4 (*ipso*-*C*, CH*Ph*$_2$), 161.5 (*ipso*-*C*, N*Ph*). ^{7}Li NMR (155.47 MHz, 298 K, C_6D_6) δ (ppm) = 0.65. Anal Calcd for $C_{31}H_{40}LiNO_3$: C, 77.31; H, 8.37; N, 2.91. Found, C, 78.03; H, 7.92; N, 2.73.

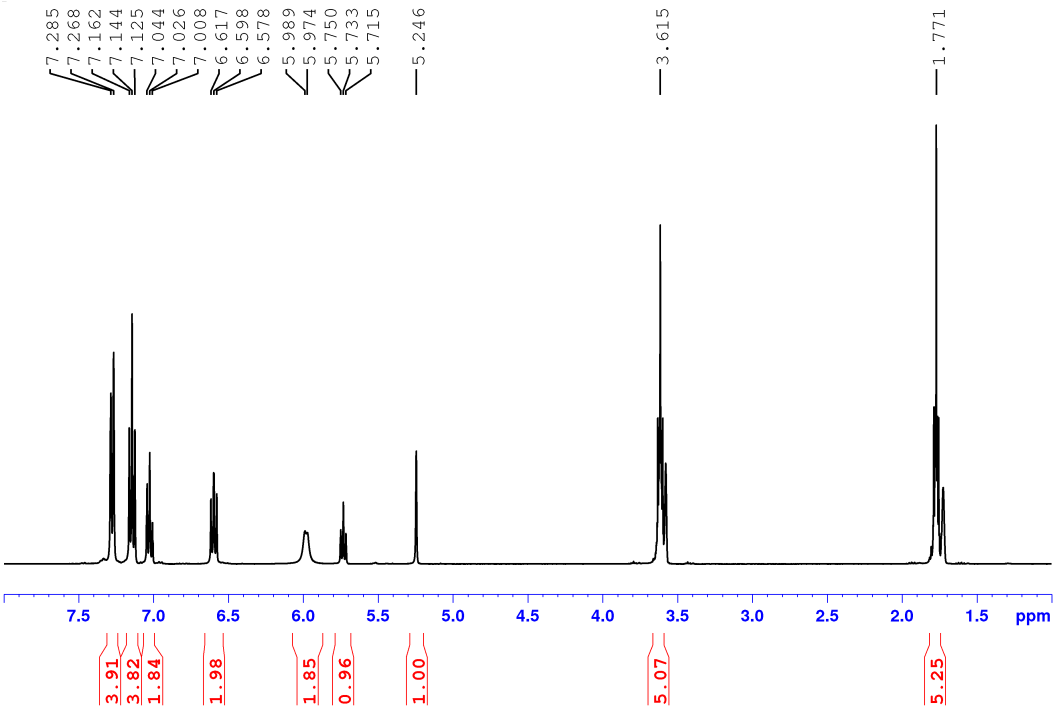

Figure ESI-25. ^{1}H NMR spectrum of compound **3** in d_8-THF at 298K.

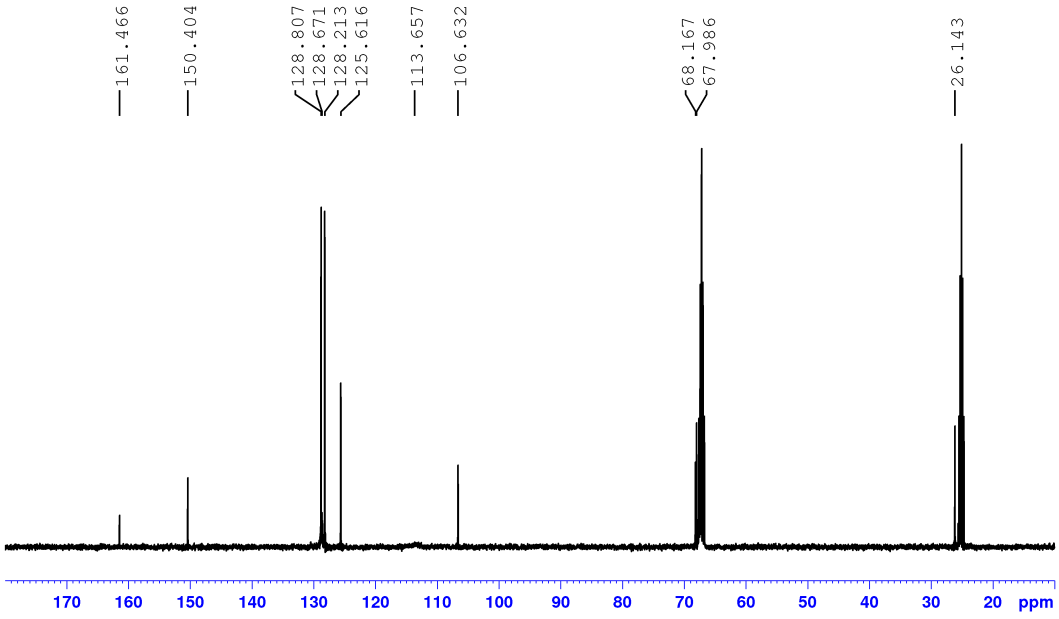

Figure ESI-26. ^{13}C NMR spectrum of compound **3** in d_8-THF at 298K.

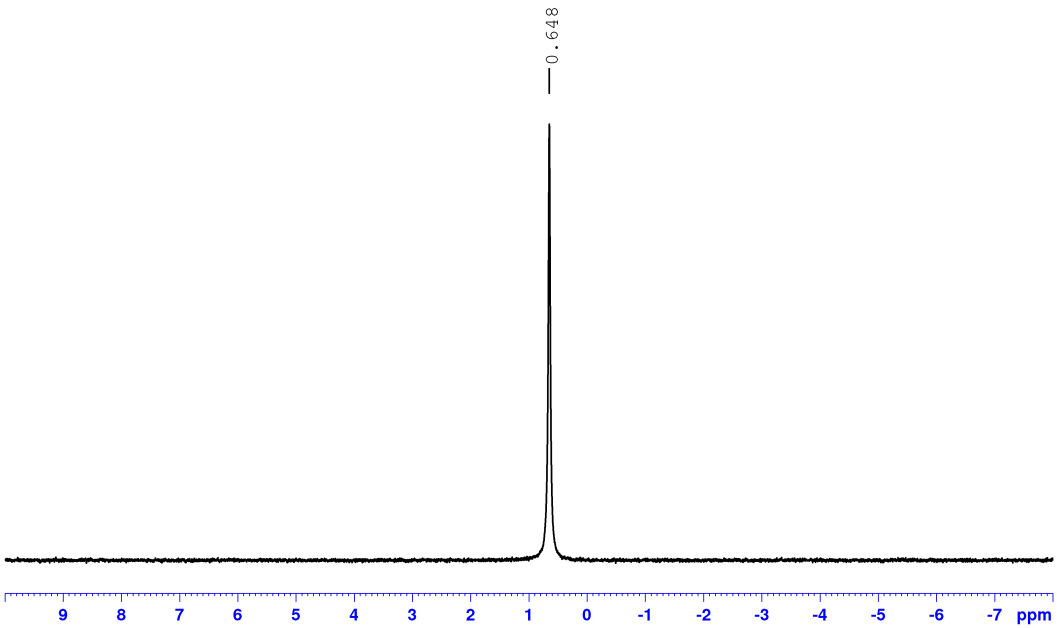

Figure ESI-27. ^{7}Li NMR spectrum of compound **3** in d_8-THF at 298K.

Addition reaction of LiPh towards PhNC(H)NPh in presence of NBu_4Cl

To a solution of PhC(H)NPh **1a** (0.0063 g, 0.035 mmol), NBu_4Cl (0.0097 g, 0.035 mmol) and $FeCp_2$ (0.005 g, 0.027 mmol) as internal standard in d_8-THF, equimolecular amounts of LiPh (0.0029, 0.035 mmol) were added. Yield for the addition product (50%) was calculated by integration of the ^{1}H NMR spectrum registered.

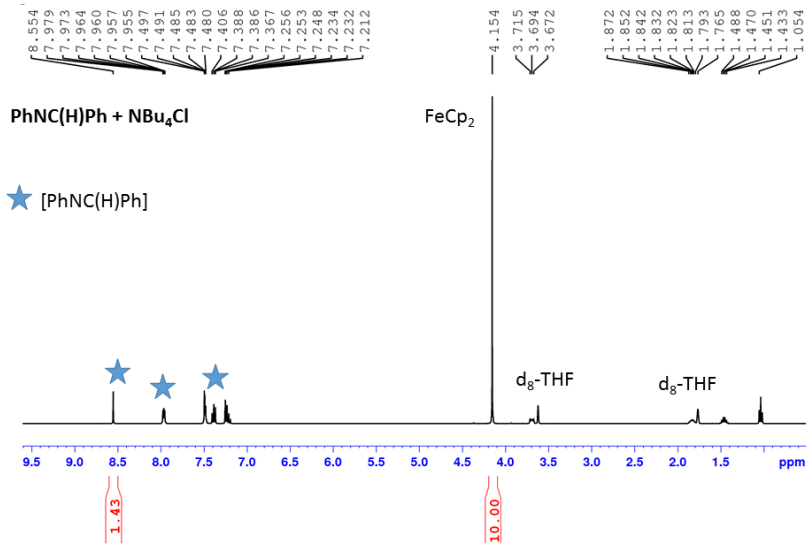

Figure ESI-28. ^{1}H NMR spectrum of the reaction mixture PhNC(H)Ph and NBu_4Cl in d_8-THF at 298K before addition of PhLi.

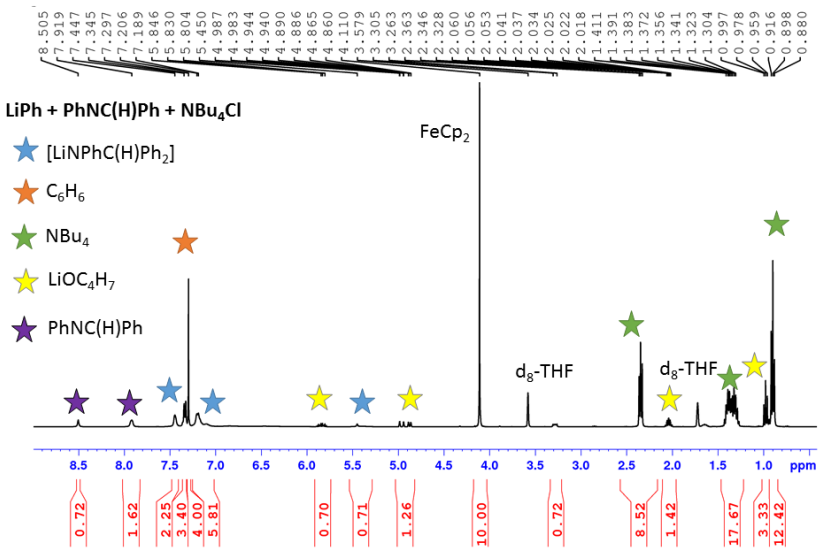

Figure ESI-29. ^{1}H NMR spectrum of the reaction mixture LiPh, NBu_4Cl and PhNC(H)Ph in d_8-THF at 298K.

DOSY Studies

To a solution of PhC(H)NPh (**1a**, 0.0063 g, 0.035 mmol), NBu_4Cl (0.0097 g, 0.035 mmol) and tetramethylsilane (4.8 µL, 0.035 mmol) as internal standard in 0.7 mL of d_8-THF, equimolecular amounts of LiPh (0.0029, 0.035 mmol) were added. The reaction mixture was investigated by ^{1}H DOSY NMR. Data were processed using the external calibration curve (ECC) for dissipated spheres and ellipsoids elaborated by Stalke.[9]

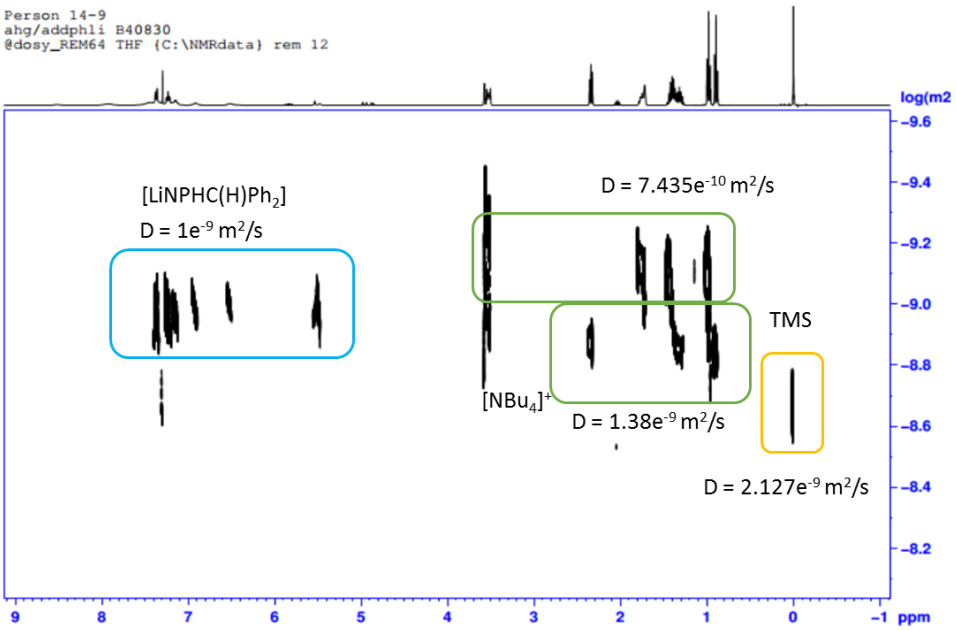

Figure ESI-30. ^{1}H DOSY NMR spectrum of the reaction mixture LiPh, NBu_4Cl and PhNC(H)Ph in d_8-THF at 298K.

Table ESI-2. Estimation of the Mw of compound generated by reaction of LiPh (40 mM), NBu_4Cl and PhNC(H)Ph in d_8-THF at 298K.

Mw estimated by ^{1}H DOSY NMR	Proposed species, Mw, (%error)	
Aromatic signals 367 g/mol	$[LiCl\{N(Ph)CHPh_2\}(THF)]^-$, 372.84 g/mol, (**2%**)	$[LiCl\{N(Ph)CHPh_2\}(THF)_2]^-$, 444.95 g/mol, (**18**%)
	$[Li\{N(Ph)CHPh_2\}(THF)_3]$, 481.61 g/mol, (**24**%)	$[Li\{N(Ph)CHPh_2\}(THF)_2]$, 409.5 g/mol, (**10**%)
	$[N(Ph)CHPh_2]^-$, 258.34 g/mol, (**-42**%)	
Alkyl signals 211 g/mol	$[NBu_4]$, 242.47 g/mol, (**13**%)	

References

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