Homologation of Isocyanates with Lithium Carbenoids: A Straightforward Access to α-Halomethyl- and α,α-Dihalomethylamides

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Abstract: Treatment of widely available isocyanates with monohalolithium and dihalolithium carbenoids provides a valuable protocol for the one-pot preparation of α-halo- and α,α-dihaloacetamide derivatives. While monohalolithium carbenoids can be prepared by a smooth lithium–halogen exchange, the preparation of the corresponding dihalo compounds proved to be highly dependent on the base used to realize the deprotonation, with lithium 2,2,6,6-tetramethylpiperidine emerging as optimal. The clear advantages of the procedure are: (a) broad scope of isocyanates that can be employed; (b) preservation of the optical purity when chiral materials are used; (c) divergent access to different haloamides by simply selecting the homologating agents. We also report an application of Charette's imidoyl triflate activation of a secondary amide to the synthesis of an α-chloro ketone and ^{15}N NMR data for selected compounds.

Key words: amides, carbenoids, lithiation, halides, nucleophilic addition

α-Haloamides and α,α-dihaloamides are versatile scaffolds in organic synthesis. In particular, the presence of the halogen atom(s) renders these structures valuable as alkylating units for a wide range of organic transformations such as the preparation of lactams or α,β-unsaturated amides.[2] Moreover, they constitute useful synthons for accessing lanthanide-based macrocycles of biological interest used as contrast agents.[3] Analogously, the corresponding α,α-dihaloamides have found various applications in synthesis,[4] e.g. as materials to obtain α-halogenated lactams.[5] Importantly, the α,α-dihaloamide moiety is found in biologically active compounds such as the broad-spectrum bacteriostatics analogues of chloramphenicol[6] or anticancer agents related to 2,2-dichloro-*N*-phenylacetamide[7] (Figure 1).

The classical approach to the synthesis of the aforementioned structures involves the reaction of an α-halo- or α,α-dihalocarboxylic acid derivative (acyl halide or ester) with an amine.[3b,8] Unfortunately, the efficiency of the procedure depends on the nucelophilicity of the amine and thus sterically hindered or less nucleophilic amines still remain challenging materials.[9] It should be observed that this tactic requires the use of substrates that are not always commercially available such as α-iodoacetyl, α,α-dibromoacetyl or α,α-diodoacetyl halides. Thus, further halogen substitutions should be performed in order to reach the desired target.[10] Moreover, more complex routes involving tandem electrophilic α,α-dihalogenations–deacylations of acetoacetanilide derivatives have been reported (e.g., Reinshagen,[11] Liu–Zhu[12] and Li–Zhang[13]) (Scheme 1).

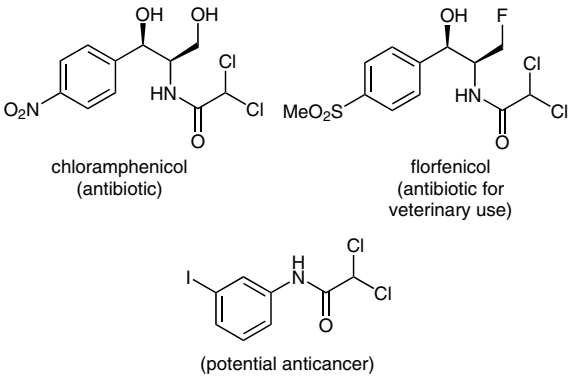
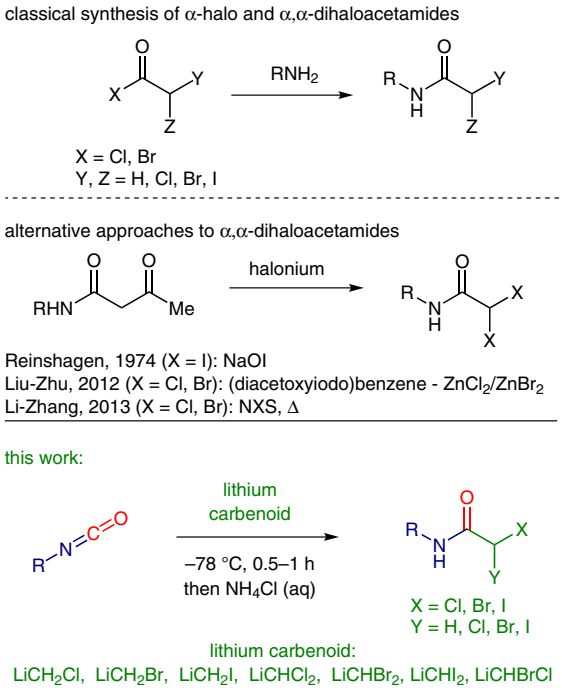


Figure 1 Versatility of haloamides in medicinal chemistry



Scheme 1 Context of the presented work

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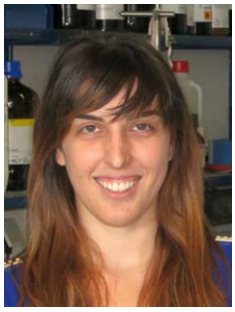
As a common feature, the introduction of the halogen through one of these methodologies takes places on a carbon atom already connected to a given array.

A distinct approach would rely on the addition of α-halomethyl or α,α-dihalomethyl carbanion-type units[14] to a proper electrophilic carbon source. Köbrich and co-workers in the late 1960s pioneered the use of halomethyllithium reagents (carbenoids);[15] these species have been thoroughly employed for homologation-type reactions of various carbonyl derivatives such as aldehydes,[16] ke-

Biographical Sketches

Vittorio Pace obtained a degree in pharmacy from the University of Perugia in 2005 working with Prof. M. Curini and Dr. O. Rosati. He then undertook Ph.D. studies (2006–2010) at the Complutense University of Madrid under the guidance of Prof. A. R. Alcántara. He realized placements at the Universities of Ghent (Belgium, Prof. N. De Kimpe), Trieste (Italy, Prof. L. Gardossi), and Graz (Austria, Prof. W. Kroutil). In 2009 he also obtained a postgraduate M.Sc. in Drug Design and Development from the University of Pavia. In 2010 he moved to the University of Vienna to join the group of Prof. W. Holzer as an Ernst Mach postdoc fellow. Postdoctoral training continued with Prof. D. J. Procter at The University Manchester (2011–2013) and with Prof. B. Olofsson at the University of Stockholm (2013–2014). In August 2014 he returned to Vienna as a group leader in Synthetic Chemistry (habilitand) at the Department of Pharmaceutical Chemistry headed by Prof. T. Langer and Prof. E. Urban. His main research interest deals with the application of lithium carbenoids and organometallic reagents in organic synthesis.

Ashenafi Damtew Mamuye was born in Alem-Ketema, Ethiopia in 1984. He completed his B.Sc. in Applied Chemistry at the University of Gondar (2006) and received his M.Sc. in medicinal chemistry from Addis Ababa University (2009). He worked as a teaching assistant from 2009 to 2011 in Ethiopia. In 2012 he joined the University of Sassari to undertake doctoral studies in chemical science and technology under the supervision of Prof. Ugo Azzena. Since October 2013, he has been a visiting Ph.D. student at the University of Vienna under the supervision of Dr. Vittorio Pace and Prof. Wolfgang Holzer. His research focuses on α-substituted organolithiums (e.g., carbenoids), arene-catalyzed lithiation, and pyrazole chemistry.



Laura Castoldi was born in 1986 in Pavia (Northern Italy): after an Erasmus placement at the Complutense University of Madrid in the group of Profs. Alcántara and Sinisterra, she graduated in Chemistry and Pharmaceutical Technology in 2011 at the University of Pavia (advisor Prof. M. Pregnolato). In 2012 she obtained a research grant from the OEAD (Austria) to spend 9 months in the group of Prof. W. Holzer to realize a postgraduate Master thesis in Drug Design and Development. Since October 2013 she has been a Uni:docs doctoral Fellow at the University of Vienna, currently working on lithium carbenoid chemistry under the guidance of Prof. Holzer and Dr. Pace.

Wolfgang Holzer studied organic chemistry at the Technical University of Vienna (Austria) where he obtained his Ph.D. in 1982. After joining the Institute of Pharmaceutical Chemistry at the University of Vienna as an assistant professor he received his habilitation in 1993 and a permanent position as associate professor in 1997. He performed a postdoctoral stay in 1989/90 at the University of Zürich (Switzerland) with Prof. W. von Philipsborn. His main research interests are the chemistry of azoles, heterocyclic tautomerism, and the application of NMR spectroscopy for structural and conformational studies.

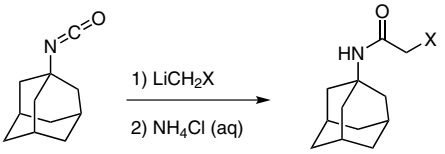
tones,[16a–c,17] N-electron-withdrawing-group substituted imines,[18] acid halides,[19] esters,[16a,20] and Weinreb amides.[9b,21] Conceptually, they are able to add a halomethylenic fragment to a reactive electrophile, thus they can be considered as functionalized organometallic reagents. Though they are regarded as ambiphilic reagents, nowadays, it is widely accepted that at low temperatures these lithium species display nucleophilic behavior.[14d,22] The main disadvantage that they possess is their well-known thermal instability. As such, three main precautions should be taken for their efficient use in synthesis: 1. generation under Barbier-type conditions (i.e., the electrophile must be present when the carbenoid is generated); 2. the use of low temperatures (–78 °C is adequate) to minimize α-elimination processes responsible for the possible degradation to a free carbene and a lithium halide salt; 3. the presence of lithium halide salts and the employment of ethereal solvents aids the preservation of the aforementioned α-elimination through a coordinative effect.[14d]

Very recently Bode and co-workers re-explored the potential of the underestimated reaction of isocyanates with Grignard reagents to access sterically hindered and electron-deficient secondary amides with high efficiency.[23] Though there are precedents in the literature using various organometallic reagents such as organolithiums,[24] organomagnesiums,[25] organocopper species,[26] organomanganese,[27] or organostannnanes,[28] it seems that this tactic has not been fully exploited as a versatile tool for amides synthesis. Inspired by this precedent[29] and by our own interest in designing transformations involving the use of lithium carbenoid reagents (e.g., $LiCH_2X$, LiCHXY),[9b,17b,21] we wondered if isocyanates could be valuable as electrophilic reagents that are susceptible to homologation with such nucleophilic lithium species. The successful method could be applied to the one-pot preparation of α-haloacetamides or α,α-dihaloacetamides starting from widely available materials such as isocyanates.

In this work we present a full account of our investigations on the halomethylation[30] and dihalomethylation of different substituted isocyanates. Pivotal for the efficiency of the reaction is the fine tuning of the generation of the carbenoids, in particular in the case of dihalomethylation. We also show the effectiveness of the procedure in homologating optically active isocyanates (without erosion of the enantiopurity) and an application of one of the so-obtained haloacetamides in the synthesis of a ketone through its transformation into an imidoyl triflate followed by the addition of a Grignard reagent.

The high sterically hindered *N*-adamantyl isocyanate **1** was identified as a model substrate for the homologation with chloromethyllithium (Table 1). According to our previously reported procedures, chloromethyllithium was generated by lithium–iodine exchange on chloroiodomethane (ICH_2Cl) performed with methyllithium–lithium bromide (entry 1). Significantly, the use of 25 mol% excess of chloroiodomethane with respect to methyllithium–lithium bromide ensures maximized formation of the carbenoid. The selection of the complex methyllithium–lithium bromide was found to be important in order to minimize degradative α-elimination on the so-formed carbenoid in agreement with pioneering studies by Villieras,[16a] confirmed more recently by our group.[9b,17b,21] An initial trial with tetrahydrofuran as the solvent and using 1.8 equivalents of chloromethyllithium afforded the desired chloroamide in 87% isolated yield (entry 1); significantly, the transformation could be efficiently accomplished also with a lower amount of carbenoid. In this sense, the use of 1.25 equivalents proved to be ideal, leaving the conversion unaffected. This observation can be explained taking into account the presumed higher reactivity of isocyanates compared to other carbon electrophiles such as Weinreb amides,[31] which required higher loading of carbenoids to maximize conversion. The coordinating

Table 1 Reaction Optimization for Monohalolithium Carbenoids



1 **2a** (X = Cl) **2b** (X = I) **2c** (X = Br)

Entry	$LiCH_2X$ (equiv)[a]	Solvent	Temp (°C)	Yield[b] (%) of **2**
1	$LiCH_2Cl$ (1.8)	THF	–78	(**2a**) 87
2	$LiCH_2Cl$ (1.5)	THF	–78	(**2a**) 86
3	$LiCH_2Cl$ (1.25)	THF	–78	(**2a**) 87
4	$LiCH_2Cl$ (1.0)	THF	–78	(**2a**) 82
5	$LiCH_2Cl$ (1.25)	MTBE	–78	(**2a**) 65
6	$LiCH_2Cl$ (1.25)	CPME	–78	(**2a**) 71
7	$LiCH_2Cl$ (1.25)	MTHF	–78	(**2a**) 76
8	$LiCH_2Cl$ (1.25)	Et_2O	–78	(**2a**) 97
9[c]	$LiCH_2Cl$ (1.25)	Et_2O	–78	(**2a**) 85
10	$LiCH_2Cl$ (1.25)[d]	Et_2O	–78	(**2a**) 82
11	$LiCH_2Cl$ (1.25)[e]	Et_2O	–78	(**2a**) 79
12	$LiCH_2Cl$ (1.25)	Et_2O	–60	(**2a**) 69
13	$LiCH_2Cl$ (1.25)	Et_2O	–50	(**2a**) 48
14	$LiCH_2I$ (1.25)	Et_2O	–78	(**2b**) 94
15	$LiCH_2Br$ (1.25)[f]	Et_2O	–78	(**2c**) 79
16	$LiCH_2Br$ (1.25)[g]	Et_2O	–78	(**2c**) 93

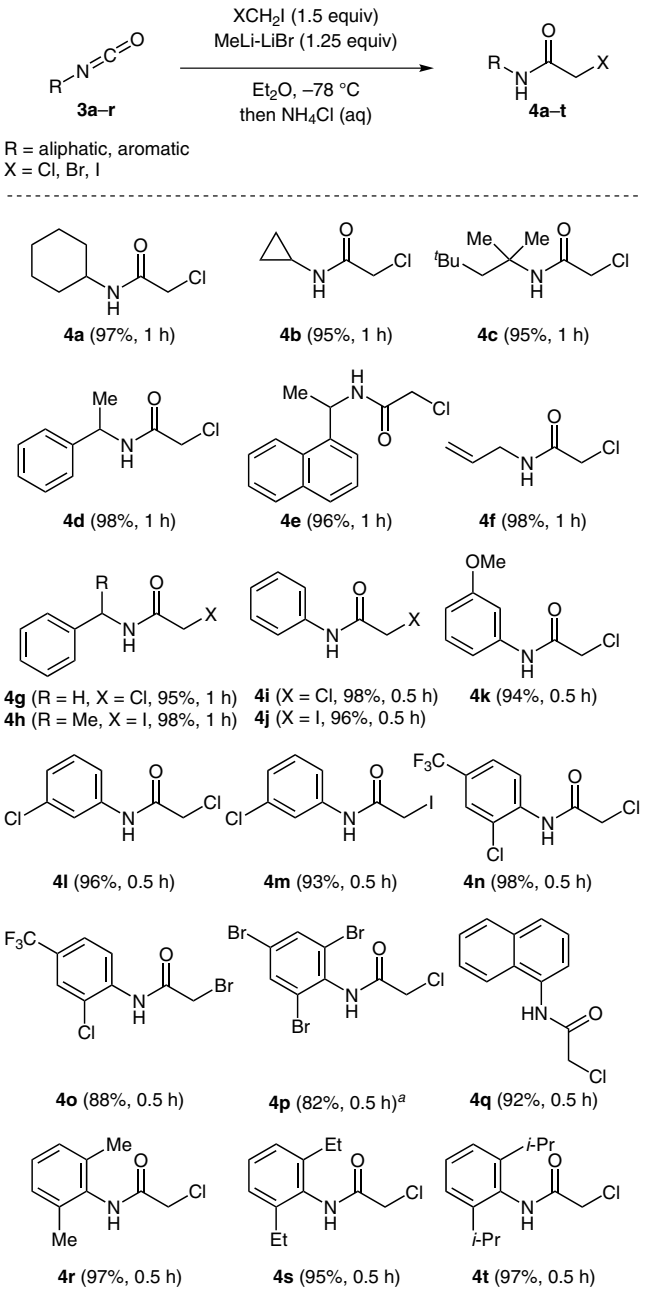
[a] Generation of $LiCH_2X$: dihalomethane (25 mol% excess), MeLi–LiBr (1.0 equiv), 1 h.
[b] Isolated yields.
[c] Reaction time 2 h.
[d] MeLi was employed as lithiating reagent.
[e] BuLi was employed as lithiating reagent.
[f] Generated from CH_2Br_2.
[g] Generated from ICH_2Br.

ability of the reaction solvent was pivotal in order to preserve its decomposition; methyl *tert*-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and 2-methyltetrahydrofuran (MTHF),[31c,32] which are considered as ecofriendly alternatives of classic ethereal solvents, provided the desired product in substantially decreased yield (entries 5–7). Switching to diethyl ether was fundamental to maximize the reactivity, giving compound **2a** in an excellent 97% yield without the need to perform additional purification (entry 8). A final remark on the generation of chloromethyllithium; using simple methyllithium or butyllithium as lithiating agents results in a decrease of in the conversion, probably because the absent lithium bromide inhibits α-elimination. By running reactions at higher temperatures a predictable decrease of the formation of **2a** was evident as a consequence of the well-known thermal instability of such species (entries 12 and 13).[14d] Reactions occurred rapidly and reached completion within a maximum of one hour; continued stirring for additional time resulted deleterious effects since unidentified materials were observed in the crude reaction mixture by ^{1}H NMR.

The process could be smoothly adapted to the preparation of the corresponding α-iodo and α-bromo derivatives **2b** and **2c**. Interestingly, we found that the optimal source of bromomethyllithium was commercially available bromoiodomethane instead of the commonly used dibromomethane due to the easier capability of the former to undergo lithium–halogen exchange compared to the latter.

After determining the ideal reaction conditions, the scope of the methodology was investigated (Scheme 2). Various (eventually highly sterically demanding) aliphatic isocyanates reacted very well providing the corresponding chloroacetamides or iodoacetamides in high yields within one hour. Interestingly, no concomitant carbenoid-mediated cyclopropanation on the olefinic fragment of an allylic substrate was observed.[33] Aromatic isocyanates worked in a similar efficient manner despite the substitution pattern on the aromatic ring. In general, they reach completion in shorter times compared to their aliphatic counterparts.[34] It is worth underlining the possibility to perform this reaction on the tribromo derivative **3p** without observing competing aryl bromide–lithium exchange. In this case, the reaction required two precautions to minimize such a collateral reaction: (a) very low temperature (–95 °C) and (b) the use of 4.0 equivalents of chloroiodomethane to generate the carbenoid. Pleasingly, the progressive increase of the steric hindrance at the *ortho* positions of 2,6-disubstituted isocyanates did not affect the efficiency of the protocol thus, permitting an easy access to chloroamides **4r**–**t**.

With the aim to expand the usefulness of the procedure, we turned our attention towards the addition of lithium dihalocarbenoids. According to the literature, the most common method to form these species is based on the deprotonation of a dihalomethane with a lithium amide base.[35] The reaction between phenyl isocyanate (**3i**) and the putative dihalomethyllithium was selected as a model



Scheme 2 Scope of the α-halomethylation reaction. Isolated yields and reaction times in parentheses. [a] ICH_2Cl (4.0 equiv), MeLi–LiBr (1.2 equiv), –95 °C.

reaction for screening (Table 2). By using the conditions developed for the corresponding α-halomethylation [CH_2Cl_2 (1.5 equiv), lithium reagent (1.25 equiv)] in the presence of lithium diisopropylamide, only urea **6a** was obtained in 84% yield with only a minimal amount (6%) of the desired α,α-dichloroamide **5** (entry 1). Modifications of the stoichiometry, reaction time, or the solvent did not have beneficial effects (entries 2–4). When the formation of the carbenoid was attempted in the absence of the electrophile, no reaction was observed at all, suggesting that its decomposition took place (entry 5). By switching to lithium dicyclohexylamide, introduced by Nozaki for

the generation of dihalocarbenoids,[35c,d] a similar competing attack of the base to the isocyanate to give urea **6b** was observed (entry 6). Because the formation of ureas through the addition of lithium amide bases is known in the literature,[36] we consider that their attack on the isocyanate is faster than the deprotonation of dichloromethane and thus the formation and reaction of dichloromethylithium with the electrophile. Running the reaction at lower temperatures (–100 °C) did not modify the reactivity profile (entry 7). Attempts to dichloromethylate **3i** adapting Izawa's procedure[37] for esters in the presence of methyllithium–lithium bromide, resulted equally in the formation of amide **7** (entry 8). Pleasingly, the use of the more sterically hindered base lithium 2,2,6,6-tetramethylpiperidide proved to be effective in avoiding the formation of urea compounds, thus allowing the chemoselective obtainment of dichloroacetamide **5** as indicated by ^{1}H NMR analysis of the crude (entry 9). Because of the lower nucleophilicity of dichloromethylithium compared to the corresponding monochloromethyllithiums, we found the use of an excess of base [CH_2Cl_2 (5 equiv), LTMP (4.5 equiv)] beneficial to maximize the yield up to 87% (entries 9–12).

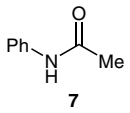


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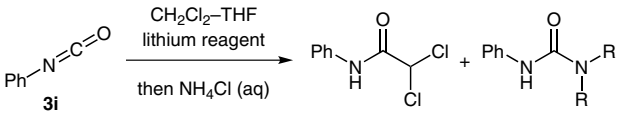
Figure 2

The dichloromethylation could be efficiently applied to various isocyanates (aromatic and aliphatic) providing compound **8a** and **8b** in very good yields (Scheme 3). Analogously, the lithium 2,2,6,6-tetramethylpiperidide assisted procedure could be employed to generate dibromo compound **8c** from dibromomethane and, the particularly challenging bromochloro derivative **8d** from bromochloromethane albeit in somewhat lower yield. Finally, by employing Bull's protocol[18c,d] for the generation of diiodomethyllithium from diiodomethane and lithium hexamethyldisilazanide we were able to prepare diiodoacetamide **8e**. It should be observed that diiodomethyllithium could be preformed prior to the addition of the isocyanate, thus indicating the higher stability of this carbenoid compared to others employed in this study that require the isocyanate to be present when the carbenoid is generated. It should be stressed that compound **8e** has been previously synthesized by Reinshagen through a complex procedure involving the degradation of acetoacetanilide with sodium hypoiodite.[11]

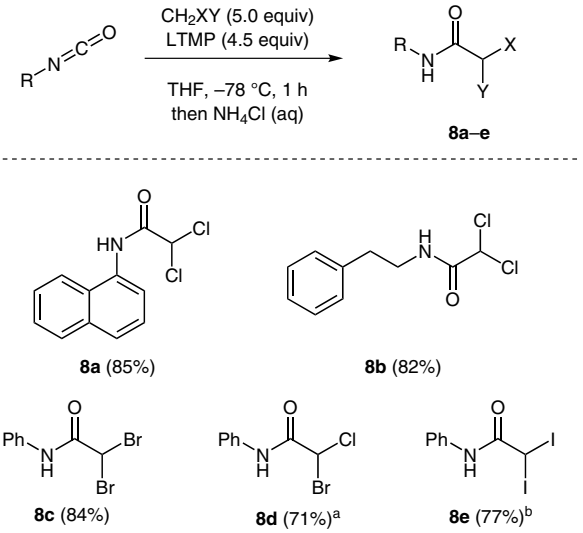
In order to gain a full insight into the studied transformation, we finally studied its adaptability to optically active isocyanates. Full preservation of the chiral information was evidenced both in the case of the addition of chloromethyllithium to give (*S*)-**4d**, (*R*)-**4e**, (*S*)-**9a**, (*R*)-**9b**, and *trans*-**9c** and dichloromethyllithium to give (*S*)-**9d** (Scheme 4).

Table 2 Reaction Optimization for the Dichloromethylation of Phenyl Isocyanate[a]

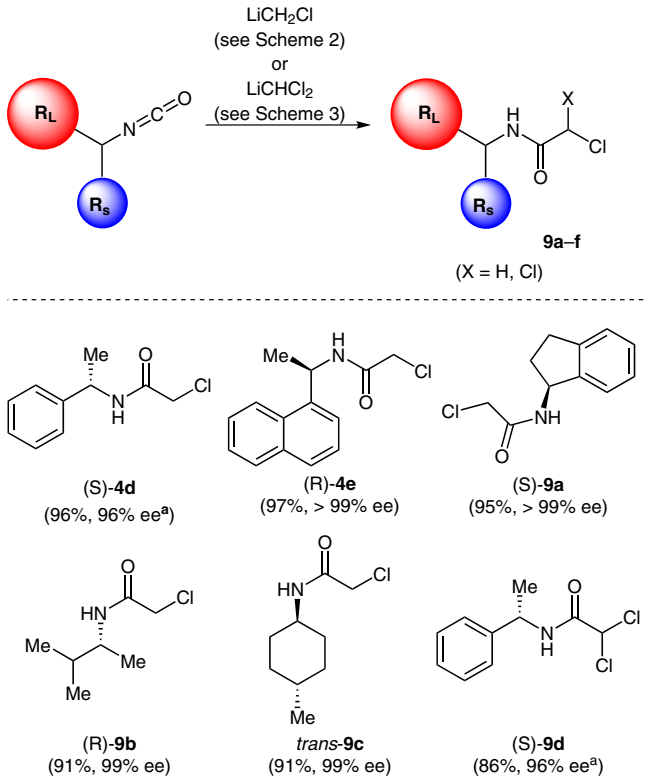


Entry	Li reagent (equiv)	CH_2Cl_2 (equiv)	Time (h)	Yield[b] (%)	
				5	**6**
1	LDA (1.25)	1.5	1	6	(**6a**) 84
2	LDA (4.5)	5.0	1	9	(**6a**) 82
3	LDA (4.5)	5.0	3	11	(**6a**) 79
4[c]	LDA (4.5)	5.0	1	8	(**6a**) 86
5[d]	LDA (4.5)	5.0	1	–	–
6	$LiNCy_2$ (4.5)	5.0	1	12	(**6b**) 78
7[e]	$LiNCy_2$ (4.5)	5.0	1	14	(**6b**) 75
8[f]	MeLi–LiBr (4.5)	5.0	1	–	–
9	LTMP (4.5)	5.0	1	87	–
10	LTMP (3.0)	5.0	1	76	–
11	LTMP (2.0)	5.0	1	71	–
12	LTMP (6.0)	8.0	1	84	–

[a] Reactions were performed at –78 °C otherwise indicated.
[b] Isolated yield.
[c] Reaction run in Et_2O.
[d] **3i** was added after 1 min from the end of the addition of LDA.
[e] Reaction run at –100 °C.
[f] Amide **7** (Figure 2) was obtained in 86% yield.



Scheme 3 Synthesis of α,α-dihaloamides. [a] Reaction time 3 h. [b] CH_2I_2 (4.4 equiv), LHDMS (4.0 equiv), THF–Et_2O (3:1), –78 °C, overnight.



Scheme 4 Application of the method to optically active isocyanates.
[a] 96% ee for the supplied starting material.

Because of our interest in the synthesis of α-halo ketone compounds,[9b,21,32h,38] we were attracted by a recent report by Charette and co-workers[39] dealing with the full chemoselective access to ketones from secondary amides via the formation of a highly electrophilic imidoyl triflate ion.[40] Pleasingly, upon activation of inert amide **4a** under such conditions, followed by the addition of benzylmagnesium chloride and acidic hydrolysis, α-halo ketone **11** was obtained in an excellent 87% yield (Scheme 5). This example broadens the scope of such a powerful strategy in allowing the addition of organometallics also to substrates bearing reactive chloromethyl functionalities. Interestingly, such a tactic allows considerable simplification of the access to ketone **11** compared to former techniques such as the Villieras' direct addition of chloromethyllithium to an ester, which had to be performed at –115 °C.[16a]

Finally, due to the lack of available information regarding ^{15}N NMR data of α-chloroamides synthesized in the course of this work, we report in Table 3 the ^{15}N chemical shifts of the amidic nitrogen for selected examples.

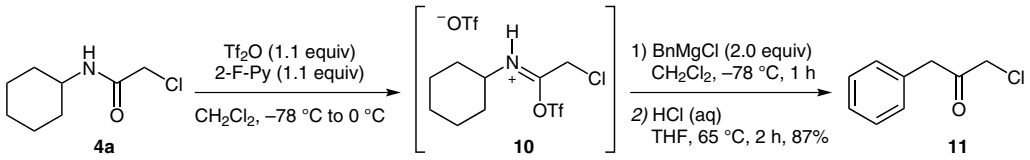
Table 3 ^{15}N NMR Data for Selected Synthesized Compounds[a]

Compound	^{15}N NMR (δ)
4b	–262.5
4n	–259.3
4o	–257.3
5	–259.3
6b	–276.1
8a	–266.4
8b	–273.5
8c	–258.3
8d	–259.2
8e[b]	–260.3
(*S*)-**9a**	–253.9
(*R*)-**9b**	–256.0
trans-**9c**	–252.7
(*S*)-**9d**	–257.3

[a] Measurements were realized in $CDCl_3$ referencing against external $MeNO_2$.
[b] DMSO-d_6 was used as the solvent.

In conclusion, we have demonstrated the effectiveness of the homologation of readily available isocyanates with lithium carbenoid (monohalo and dihalo) reagents to produce the corresponding secondary amide adducts through a simple nucleophilic addition. The method is particularly attractive compared to the usual procedures used to prepare these substrates because: 1. it does not rely on the nucleophilicity of the amine as occurs in the case of condensation with haloacetyl halides; 2. steric hindrance on the isocyanate does not affect the overall transformation; 3. the protocol can be smoothly adapted to the synthesis of the desired haloamides by correct selection of the isocyanate and the carbenoid; 4. with chiral isocyanates no erosion of the optical purity of reaction products was observed.

^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectra were recorded on a Bruker AC-250 spectrometer (250 MHz for ^{1}H, 62.5 MHz for ^{13}C, and 235 MHz for ^{19}F) or on a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, and 40 MHz for ^{15}N) or a Bruker Avance 500 spectrometer (500 MHz for ^{1}H, 126 MHz for ^{13}C) from $CDCl_3$ solutions at 25 °C. The center of the (residual) sol-



Scheme 5 Addition of benzylmagnesium chloride to an α-chloroamide via activation as imidoyl triflate

vent signal was used as an internal standard which was related to TMS with δ = 7.26 (^{1}H, $CDCl_3$), δ 77.0 (^{13}C, $CDCl_3$), δ = 2.49 (^{1}H, DMSO-d_6), δ = 39.5 (^{13}C, DMSO-d_6), δ = 2.05 (^{1}H, acetone-d_6), and δ = 29.8 (^{13}C, acetone-d_6). With the ^{19}F NMR spectra absolute referencing via Ξ ratio was performed. ^{15}N NMR spectra were referenced against external $MeNO_2$. Chiral HPLC was carried out with Chiralcel OD-H, or Chiralpak IA columns, as indicated. IR absorption spectra were recorded as NaCl pellets on a Shimadzu FT-IR 8400S (E41107) instrument. Spectra analyses were performed with the software Shimadzu IRsolution (Version 1.21, 2005). Elementary microanalyses were carried out using a Leco CHNS 932 equipment. Column chromatography purifications were conducted on silica gel 60 (40–63 μm). Melting points are uncorrected. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column (EtOAc–hexane, unless otherwise specified). TLC was carried out on aluminum sheets precoated with silica gel 60F_{254} (Macherey-Nagel, Merk); the spots were visualized under UV light (λ = 254 nm) and/or aq $KMnO_4$ was used as the developing system. All chemicals were purchased from Sigma Aldrich, Acros, Alfa Aesar, and TCI and solvents were purified by distillation immediately before use according to standard procedures. Dihalomethanes used as carbenoids precursors and amine bases (*i*-Pr_2NH and 2,2,6,6-tetramethylpiperidine) were distilled immediately before use.

Chemoselective Addition of Lithium Carbenoids to Isocyanates; General Procedure 1 (GP1)

To a cooled (–78 °C) solution of isocyanate (1.0 equiv) in dry Et_2O (1 M concentration) was added the dihalomethane derivative (1.5 equiv). After 2 min, an ethereal solution of 1.5 M MeLi–LiBr (1.25 equiv) was added dropwise over 5 min. The resulting solution was stirred for the appropriate time (see Table 1 and Scheme 2) at that temperature. Sat. aq NH_4Cl was added (2 mL/mmol substrate) and the cooling bath was removed, the mixture was stirred till it reached r.t., and then it was extracted with additional Et_2O (2 × 5 mL) and washed with water (5 mL) and brine (10 mL). The organic phase was dried (anhyd Na_2SO_4), filtered, and the solvent removed under reduced pressure to give pure samples of haloacetamides.

***N*-(Chloroacetyl)adamantan-1-amine (2a)**[30]

By following GP1, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **2a** (839 mg, 97%) as a white solid; mp 119 °C.

IR (NaCl): 3239, 3080, 2108, 1662, 1569, 1234 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.22 (br s, 1 H), 3.90 (s, 2 H), 2.12–2.03 (m, 3 H), 2.03–1.95 (m, 6 H), 1.66 (t, *J* = 2.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.5, 52.3, 42.8, 41.1, 36.1, 29.3.

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.42; H, 8.09; N, 6.27.

***N*-(Iodoacetyl)adamantan-1-amine (2b)**[30]

By following GP1, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), CH_2I_2 (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O give **2b** (1140 mg, 94%) as a yellow solid; mp 121–123 °C.

IR (NaCl): 3250, 1664, 1570, 1230, 996 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.17 (s, 1 H), 3.60 (s, 2 H), 2.22–1.81 (m, 9 H), 1.77–1.57 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 52.7, 41.2, 36.4, 29.4, 1.6.

Anal. Calcd for $C_{12}H_{18}INO$: C, 45.16; H, 5.68; N, 4.39. Found: C, 45.31; H, 5.75; N, 4.52.

***N*-(Bromoacetyl)adamantan-1-amine (2c)**[30]

By following GP1, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), ICH_2Br (1.26 g, 0.43 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **2b** (962 mg, 93%) as a white solid; mp 124 °C.

IR (NaCl): 3243, 2105, 1661, 1572, 1232 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.12 (br s, 1 H), 3.77 (s, 2 H), 2.10 (s, 3 H), 2.01 (d, *J* = 3.0 Hz, 6 H), 1.69 (t, *J* = 6.3 Hz, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.1, 52.5, 41.1, 36.2, 29.9, 29.3.

Anal. Calcd for $C_{12}H_{18}BrNO$: C, 52.95; H, 6.67; N, 5.15. Found: C, 53.09; H, 6.82; N, 5.30.

2-Chloro-*N*-cyclohexylacetamide (4a)[30]

By following GP1, starting from cyclohexyl isocyanate (0.47 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4a** (647 mg, 97%) as a white solid; mp 113 °C.

IR (NaCl): 3241, 1651, 1567, 1223 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (br s, 1 H), 3.96 (s, 2 H), 3.73–3.69 (m, 1 H), 1.87–1.84 (m, 2 H), 1.65–1.63 (m, 2 H), 1.5–1.53 (m, 1 H), 1.33–1.29 (m, 2 H), 1.16–1.13 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.8, 48.6, 42.7, 32.8, 25.4, 24.7.

Anal. Calcd for $C_8H_{14}ClNO$: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.83; H, 8.14; N, 8.12.

2-Chloro-*N*-cyclopropylacetamide (4b)[30]

By following GP1, starting from cyclopropyl isocyanate (0.32 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4b** (480 mg, 95%) as a white solid; mp 77 °C.

IR (NaCl): 3246, 1648, 1230, 990 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (br s, 1 H, NH), 4.01 (s, 2 H, CH_2Cl), 2.74 (m, 1 H, NCH), 0.82 (m, 2 H, CH_2CH_2), 0.57 (m, 2 H, CH_2CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2 (C=O), 42.5 (CH_2Cl), 22.8 (NCH), 6.4 (CH_2CH_2).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –262.5 (amide).

Anal. Calcd for C_5H_8ClNO: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.15; H, 6.23; N, 10.24.

2-Chloro-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (4c)[30]

By following GP1, starting from 2-isocyanato-2,4,4-trimethylpentane (0.59 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4c** (740 mg, 95%) as a white solid; mp 38–40 °C.

IR (NaCl): 3251, 1656, 1236, 907 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.43 (s, 1 H), 3.90 (s, 2 H), 1.50–1.29 (m, 7 H), 1.06–0.92 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.6, 55.8, 51.9, 43.1, 32.9, 31.8, 31.5, 31.2, 29.4, 28.8.

Anal. Calcd for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; N, 6.81. Found: C, 58.19; H, 9.95; N, 6.68.

2-Chloro-*N*-(1-phenylethyl)acetamide (4d)[30]

By following GP1, starting from α-methylbenzyl isocyanate (0.56 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4d** (736 mg, 98%) as a white solid; mp 100 °C.

IR (NaCl): 3260, 2974, 1652, 1542, 1230, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.18 (m, 5 H), 6.74 (s, 1 H), 5.05 (quint., *J* = 7.0 Hz, 1 H), 3.98 (m, 2 H), 1.46 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.0, 144.2, 128.8, 127.3, 125.8, 49.3, 42.7, 21.7.

Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.89; H, 6.29; N, 7.24.

2-Chloro-*N*-[1-(1-naphthyl)ethyl]acetamide (4e)[30]
By following GP1, starting from 1-(1-naphthyl)ethyl isocyanate (0.75 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4e** (913 mg, 96%) as a white solid; mp 140 °C.

IR (NaCl): 3284, 1649, 1537, 1231 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.5 Hz, 1 H), 7.92 (d, *J* = 8.6 Hz, 1 H,), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.56 (m, 4 H), 6.81 (s, 1 H), 4.15 (s, 2 H), 1.74 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.4, 137.0, 133.5, 130.5, 128.5, 128.2, 126.2, 125.5, 124.8, 122.6, 122.1, 44.8, 42.2, 20.4.

Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.99; H, 5.87; N, 5.82.

***N*-Allyl-2-chloroacetamide (4f)**[30]
By following GP1, starting from allyl isocyanate (0.32 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4f** (508 mg, 98%) as a light orange oil.

IR (NaCl): 3294, 1662, 1542, 1419, 1261, 992 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.69 (br s, 1 H), 5.82–5.74 (m, 1 H), 5.18–5.10 (m, 2 H), 4.00 (s, 2 H), 3.88–3.86 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.8, 133.2, 115.7, 42.0, 41.1.

Anal. Calcd for C_5H_8ClNO: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.11; H, 6.21; N, 10.68.

***N*-Benzyl-2-chloroacetamide (4g)**[30]
By following GP1, starting from benzyl isocyanate (0.50 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4g** (663 mg, 95%) as a white solid; mp 95 °C.

IR (NaCl): 3286, 1658, 1535, 994 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.16 (m, 5 H), 6.81 (br s, 1 H), 4.42 (d, *J* = 6.1 Hz, 2 H), 4.02 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 137.3, 128.8, 127.9, 127.8, 43.9, 42.6.

Anal. Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 59.11; H, 5.65; N, 7.84.

2-Iodo-*N*-(1-phenylethyl)acetamide (4h)
By following the general procedure, starting from α-methylbenzyl isocyanate (0.56 g, 3.8 mmol), CH_2I_2 (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4h** (1099 mg, 98%) as a light yellow solid; mp 118 °C.

IR (NaCl): 3298, 1655, 1551, 994 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.93 (br s, 1 H), 7.33–7.13 (m, 5 H), 4.99–4.93 (m, 1 H), 3.71 (m, 2 H), 1.37 (m, 3 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 167.0, 144.6, 128.8, 127.3, 126.6, 49.5, 22.0, 0.0.

Anal. Calcd for $C_{10}H_{12}INO$: C, 41.54; H, 4.18; N, 4.84. Found: C, 41.63; H, 4.32; N, 5.01.

2-Chloro-*N*-phenylacetamide (4i)
By following GP1, starting from phenyl isocyanate (0.45 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4i** (632 mg, 98%) as a white solid; mp 134 °C (Lit.[8] 134–135 °C).

IR (NaCl): 3262, 1651, 1546, 1235, 990, 907 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H), 7.63–7.49 (m, 2 H), 7.47–7.30 (m, 2 H), 7.24–7.02 (m, 1 H), 4.18 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.0, 136.8, 129.2, 125.4, 120.3, 43.0.

Anal. Calcd for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.81; H, 4.93; N, 8.12.

2-Iodo-*N*-phenylacetamide (4j)[30]
By following GP1, starting from phenyl isocyanate (0.45 g, 3.8 mmol), CH_2I_2 (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4j** (952 mg, 96%) as a white solid; mp 145 °C.

IR (NaCl): 3271, 1647, 1241, 992 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.86 (br s, 1 H), 7.62–7.43 (m, 2 H), 7.43–7.28 (m, 2 H), 7.21–7.05 (m, 1 H), 3.86 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.3, 129.2, 125.2, 120.1, 0.1.

Anal. Calcd for C_8H_8INO: C, 36.81; H, 3.09; N, 5.37. Found: C, 36.81; H, 3.09; N, 5.37.

2-Chloro-*N*-(3-methoxyphenyl)acetamide (4k)[30]
By following GP1, starting from 3-methoxyphenyl isocyanate (0.57 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4k** (713 mg, 94%) as a white solid; mp 93 °C.

IR (NaCl): 3291, 1661, 1543, 1376, 1254 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (br s, 1 H), 7.21–7.15 (m, 2 H), 6.94 (m, 1 H), 6.67–6.64 (m, 1 H), 4.11 (s, 2 H), 3.74 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 160.3, 137.8, 129.9, 112.2, 111.0, 105.9, 55.4, 42.9.

Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.33; H, 5.23; N, 7.27.

2-Chloro-*N*-(3-chlorophenyl)acetamide (4l)[30]
By following GP1, starting from 3-chlorophenyl isocyanate (0.58 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4l** (744 mg, 96%) as a white solid; mp 100 °C.

IR (NaCl): 3278, 1661, 1267, 990 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.29 (br s, 1 H), 7.69 (t, *J* = 2.0 Hz, 1 H), 7.51–7.28 (m, 2 H), 7.25–7.10 (m, 1 H), 4.21 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.3, 138.2, 135.3, 130.6, 125.8, 120.6, 118.5, 43.2.

Anal. Calcd for $C_8H_7C_{l2}NO$: C, 47.09; H, 3.46; Cl, 34.75; N, 6.86; O, 7.84.

***N*-(3-Chlorophenyl)-2-iodoacetamide (4m)**[30]
By following GP1, starting from 3-chlorophenyl isocyanate (0.58 g, 3.8 mmol), CH_2I_2 (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4m** (1.044 g, 93%) as a white solid; mp 84–85 °C.

IR (NaCl): 3289, 1659, 909 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.99 (br s, 1 H), 7.66 (t, *J* = 1.9 Hz, 1 H), 7.46–7.28 (m, 2 H), 7.16 (dt, *J* = 7.8, 1.6 Hz, 1 H), 3.90 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 138.8, 135.2, 130.5, 125.5, 120.5, 118.4, 0.0.

Anal. Calcd for C_8H_7ClINO: C, 32.52; H, 2.39; N, 4.74. Found: C, 32.39; H, 2.21; N, 4.88.

2-Chloro-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (4n)
By following GP1, starting from 2-chloro-4-(trifluoromethyl)phenyl isocyanate (0.80 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4n** (1.013 g, 98%) as a white solid; mp 64–65 °C.

IR (NaCl): 3293, 1664, 1242, 990 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.01 (br s, 1 H, NH), 8.73 (d, *J* = 2.0 Hz, 1 H, $H6_{Ph}$), 7.51 (m, 1 H, $H3_{Ph}$), 7.34 (m, 1 H, $H4_{Ph}$), 4.25 (s, 2 H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1 (C=O), 134.2 ($C1_{Ph}$), 130.3 (q, *J* = 33.2 Hz, $C5_{Ph}$), 129.6 ($C3_{Ph}$), 123.4 (q, *J* = 272.6 Hz, CF_3), 121.9 (q, *J* = 3.8 Hz, $C4_{Ph}$), 117.9 (q, *J* = 4.0 Hz, $C6_{Ph}$), 44.0 (CH_2Cl).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –259.3 (amide).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –62.4 (q, *J* = 0.7 Hz, CF_3).

Anal. Calcd for $C_9H_6Cl_2F_3NO$: C, 39.73; H, 2.22; N, 5.15. Found: C, 39.56; H, 2.07; N, 5.29.

2-Bromo-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (4o)[30]
By following GP1, starting from 2-chloro-4-(trifluoromethyl)phenyl isocyanate (0.80 g, 3.8 mmol), ICH_2Br (1.26 g, 0.43 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4o** (1.21 g, 88%) as a white solid; mp 87–88 °C.

IR (NaCl): 3288, 1662, 1246, 996, 910 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.89 (br s, 1 H, NH), 8.71 (d, *J* = 1.8 Hz, 1 H, $H6_{Ph}$), 7.52 (d, *J* = 8.4 Hz, 1 H, $H3_{Ph}$), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1 H, $H4_{Ph}$), 4.09 (s, 2 H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6 (C=O), 134.5 ($C1_{Ph}$), 130.3 (q, *J* = 33.2 Hz, $C5_{Ph}$), 129.6 ($C3_{Ph}$), 126.6 ($C2_{Ph}$), 123.4 (q, *J* = 272.5 Hz, CF_3), 121.9 (q, *J* = 3.8 Hz, $C4_{Ph}$), 117.9 (q, *J* = 4.0 Hz, $C6_{Ph}$), 29.4 (CH_2Br).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –257.3 (amide).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –62.7 (s, CF_3).

Anal. Calcd for $C_9H_6BrClF_3NO$: C, 34.15; H, 1.91; N, 4.43. Found: C, 34.27; H, 2.00; N, 4.51.

2-Chloro-*N*-(2,4,6-tribromophenyl)acetamide (4p)[30]
By following GP1, starting from 2,4,6-tribromophenyl isocyanate (1.46 g, 3.8 mmol), ICH_2Cl (2.68 g, 1.11 mL, 15.2 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O (at –95 °C) gave **4p** (1.27 g, 82%) as a white solid; mp 221–222 °C.

IR (NaCl): 3287, 1660, 998 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (br s, 1 H, NH), 7.78 (s, 2 $H_{,}$), 4.26 (s, 2 H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1 (C=O), 134.9 ($C3_{Ph}$, $C5_{Ph}$), 133.0 ($C1_{Ph}$), 124.1 ($C2_{Ph}$, $C6_{Ph}$), 122.4 ($C4_{Ph}$), 42.7 (CH_2Cl).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –257.8 (amide).

Anal. Calcd for $C_8H_5Br_3ClNO$: C, 23.65; H, 1.24; N, 3.45. Found: C, 23.72; H, 1.30; N, 3.60.

2-Chloro-*N*-(1-naphthyl)acetamide (4q)[30]
By following GP1, starting from 1-naphthyl isocyanate (0.64 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4q** (768 mg, 92%) as a white solid; mp 154 °C.

IR (NaCl): 3273, 2963, 1663, 1552, 1509, 1399, 1270, 1251 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.78 (br s, 1 H), 7.98 (d, *J* = 7.5 Hz, 1 H), 7.88 (m, 2 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.58–7.51 (m, 3 H), 4.36 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 134.1, 131.2, 128.9, 126.9, 126.7, 126.5, 126.2, 125.7, 120.6, 120.2, 43.3.

Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.80; H, 4.77; N, 6.59.

2-Chloro-*N*-(2,6-dimethylphenyl)acetamide (4r)[30]
By following GP1, starting from 2,6-dimethylphenyl isocyanate (0.56 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4r** (729 mg, 97%) as a white solid; mp 140 °C.

IR (NaCl): 3266, 2975, 1655, 1588, 1331, 1251, 997 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (br s, 1 H), 7.15–7.10 (m, 3 H), 4.26 (s, 2 H), 2.25 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 135.4, 132.7, 128.4, 127.9, 42.8, 18.3.

Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.91; H, 6.31; N, 7.22.

2-Chloro-*N*-(2,6-diethylphenyl)acetamide (4s)[30]
By following GP1, starting from 2,6-diethylphenyl isocyanate (0.66 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4s** (815 mg, 95%) as a white solid; mp 201 °C.

IR (NaCl): 3259, 2970, 2873, 1657, 1592, 1470, 1330, 1247 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.19–7.04 (m, 3 H), 4.13 (s, 2 H), 2.49 (q, *J* = 6.4 Hz, 4 H), 1.11 (t, *J* = 6.4 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 141.4, 131.6, 128.5, 126.5, 42.8, 24.8, 14.4.

Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found: C, 64.00; H, 7.22; N, 6.35.

2-Chloro-*N*-(2,6-diisopropylphenyl)acetamide (4t)[30]
By following GP1, starting from 2,4-diisopropylphenyl isocyanate (0.77 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **4t** (935 mg, 97%) as a white solid; mp 149 °C.

IR (NaCl): 3248, 1678, 1660, 1533, 998 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 7.46–7.20 (m, 3 H), 4.30 (s, 2 H), 3.07 (sept, *J* = 6.9 Hz, 2 H), 1.26 (d, *J* = 6.9 Hz, 12 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.5, 146.1, 130.1, 129.0, 123.8, 42.9, 28.9, 23.7.

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.09; H, 8.10; N, 5.69.

Dichloromethylation of Phenyl Isocyanate with Lithium Diisopropylamide and Lithium Dicyclohexylamide; General Procedure 2
A 1.5 M MeLi–LiBr solution (3.0 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of the corresponding amine (4.5 equiv) in THF (4 mL) at 0 °C.[32f] The generated lithium amide was transferred to a cooled (–78 °C) solution of phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol, 1.0 equiv) and CH_2Cl_2 (425 mg, 0.32 mL, 5.0 mmol, 5.0 equiv) in dry THF (1 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq NH_4Cl was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred till it reached r.t. and then extracted with additional Et_2O (2 × 5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd Na_2SO_4), filtered, and, after removal of the solvent under reduced pressure, afforded a mixture of compounds **5** and **6a** or **6b** (Table 2).

2,2-Dichloro-*N*-phenylacetamide (5; Table 2, Entry 9)
Yield: 177 mg (87%); white solid; mp 106–107 °C (Lit.[41] 109 °C).

IR (NaCl): 1673, 1601, 1498 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br s, 1 H, NH), 7.56 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.39 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.21 (m, 1 H, $H4_{Ph}$), 6.05 (s, 1 H, Cl_2CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7 (C=O), 136.2 ($C1_{Ph}$), 129.2 ($C3_{Ph}$, $C5_{Ph}$), 125.7 ($C4_{Ph}$), 120.2 ($C2_{Ph}$, $C6_{Ph}$), 66.9 (Cl_2CH).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –259.3 (NH).

1,1-Diisopropyl-3-phenylurea (6a; Table 2, Entry 4)
Yield: 189 mg (86%); white solid; mp 112–114 °C (Lit.[42] 114–116 °C).

IR (NaCl): 1632, 1521, 1445, 1332, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.28 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.01 (m, 1 H, $H4_{Ph}$), 6.18 (br s, 1 H, NH), 3.99 (sept, J = 6.9 Hz, 2 H, C*H*Me_2), 1.34 [br s, 12 H, CH(CH_3)$_2$].

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.6 (C=O), 139.3 ($C1_{Ph}$), 128.9 ($C3_{Ph}$, $C5_{Ph}$), 122.6 ($C4_{Ph}$), 119.7 ($C2_{Ph}$, $C6_{Ph}$), 45.4 (*C*HMe_2), 21.5 [CH(*C*H$_3$)$_2$].

^{15}N NMR (40 MHz, $CDCl_3$): δ = –276.4 (PhNH), –268.2 (*i*-PrN).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.93; H, 9.31; N, 12.86.

1,1-Dicyclohexyl-3-phenylurea (6b; Table 2, Entry 6)
Yield: 234 mg (78%); white solid; mp 170–171 °C.

IR (NaCl): 1635, 1520 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.27 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.00 (m, 1 H, $H4_{Ph}$), 6.25 (br s, 1 H, NH), 3.48 (m, 2 H, $H1_{Cy}$), 1.84 (m, 4 H, $H3_{Cy}$, $H5_{Cy}$), 1.76 (m, 8 H, $H2_{Cy}$, $H6_{Cy}$), 1.68 (m, 2 H, $H4_{Cy}$), 1.35 (m, 4 H, $H3'_{Cy}$, $H5'_{Cy}$), 1.14 (m, 2 H, $H4'_{Cy}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.9 (C=O), 139.4 ($C1_{Ph}$), 128.8 ($C3_{Ph}$, $C5_{Ph}$), 122.5 ($C4_{Ph}$), 119.6 ($C2_{Ph}$, $C6_{Ph}$), 55.4 ($C1_{Cy}$), 31.9 ($C2_{Cy}$, $C6_{Cy}$), 26.4 ($C3_{Cy}$, $C5_{Cy}$), 25.5 ($C4_{Cy}$).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –276.1 (NH), CyN not found.

Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 76.09; H, 9.48; N, 9.40.

Chemoselective Addition of Lithium Polyhalocarbenoids to Isocyanates; General Procedure 3
A 1.5 M MeLi–LiBr solution (3.0 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of 2,2,6,6-tetramethylpiperidine (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) in THF (4 mL) at 0 °C. The generated LTMP was transferred to a cooled (–78 °C) solution of the isocyanate (1.0 equiv) and dihalomethane (5.0 equiv) in dry THF (1 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq NH_4Cl was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred until it reached r.t. and then extracted with additional Et_2O (2 × 5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd Na_2SO_4), filtered and, after removal of the solvent under reduced pressure, the so-obtained crude mixture was subjected to chromatography (silica gel) to afford pure dihaloamides.

2,2-Dichloro-*N*-(1-naphthyl)acetamide (8a)
By following GP3, starting from 1-naphthyl isocyanate (0.14 mL, 169 mg, 1.0 mmol) and CH_2Cl_2 (425 mg, 0.32 mL, 5.0 mmol) in THF (1 mL) with chromatography (silica gel, petroleum ether–EtOAc, 8:2, R_f = 0.4) gave **8a** (216 mg, 85%) as a colorless solid; mp 135–137 °C.

IR (NaCl): 1675, 1605 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H, NH), 7.90 (m, 1 H $H5_{Naphth}$), 7.88 (m, 1 H, $H2_{Naphth}$), 7.86 (m, 1 H, $H8_{Naphth}$), 7.78 (m, 1 H, $H4_{Naphth}$), 7.58 (m, 1 H, $H7_{Naphth}$), 7.54 (m, 1 H, $H6_{Naphth}$), 7.49 (m, 1 H, $H3_{Naphth}$), 6.17 (s, 1 H, $CHCl_2$).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.6 (C=O), 134.0 ($C4a_{Naphth}$), 130.4 ($C1_{Naphth}$), 128.9 ($C5_{Naphth}$), 127.2 ($C8a_{Naphth}$), 127.1 ($C4_{Naphth}$), 126.9 ($C7_{Naphth}$), 126.4 ($C6_{Naphth}$), 125.6 ($C3_{Naphth}$), 121.2 ($C2_{Naphth}$), 120.2 ($C8_{Naphth}$), 67.1 ($CHCl_2$).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –266.4 (NH).

Anal. Calcd for $C_{12}H_9Cl_2NO$: C, 56.72; H, 3.57; N, 5.51. Found: C, 56.81; H, 3.60; N, 5.58.

2,2-Dichloro-*N*-(2-phenylethyl)acetamide (8b)
By following GP3, starting from phenethyl isocyanate (0.14 mL, 147 mg, 1.0 mmol) and CH_2Cl_2 (425 mg, 0.32 mL, 5.0 mmol) in THF (1 mL) with chromatography (silica gel, petroleum ether–EtOAc, 8:2, R_f = 0.45) gave **8b** (190 mg, 82%) as a colorless solid; mp 67–68 °C.

IR (NaCl): 1667, 1598, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.26 (m, 1 H, $H4_{Ph}$), 7.22 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 6.57 (br s, 1 H, NH), 5.89 (s, 1 H, Cl_2CH), 3.59 (m, 2 H, NHCH_2), 2.88 (t, J = 7.0 Hz, 2 H, PhCH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.0 (C=O), 138.0 ($C1_{Ph}$), 128.8 ($C2_{Ph}$, $C6_{Ph}$), 128.7 ($C3_{Ph}$, $C5_{Ph}$), 126.8 ($C4_{Ph}$), 66.4 (Cl_2CH), 41.5 (NH*C*H$_2$), 35.2 (Ph*C*H$_2$).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –273.5 (NH).

Anal. Calcd for $C_{10}H_{11}Cl_2NO$: C, 51.75; H, 4.78; N, 6.03. Found: C, 51.87; H, 4.90; N, 6.13.

2,2-Dibromo-*N*-phenylacetamide (8c)[13]
By following GP3, starting from phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol) and CH_2Br_2 (869 mg, 0.35 mL, 5.0 mmol) in THF (1 mL), with chromatography (silica gel, petroleum ether–EtOAc, 8:2, R_f = 0.45) gave **8c** (246 mg, 84%) as a colorless solid; mp 115–117 °C.

IR (NaCl): 1670, 1601, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br s, 1 H, NH), 7.55 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.38 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.20 (m, 1 H, $H4_{Ph}$), 5.94 (s, 1 H, Br_2CH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.1 (C=O), 136.5 ($C1_{Ph}$), 129.2 ($C3_{Ph}$, $C5_{Ph}$), 125.6 ($C4_{Ph}$), 120.1 ($C2_{Ph}$, $C6_{Ph}$), 36.7 (Br_2CH).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –258.3 (NH).

Anal. Calcd for $C_8H_7Br_2NO$: C, 32.80; H, 2.41; N, 4.78. Found: C, 32.91; H, 2.48; N, 4.85.

2-Bromo-2-chloro-*N*-phenylacetamide (8d)[43]
By following GP3, starting from phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol) and $ClCH_2Br$ (647 mg, 0.33 mL, 5.0 mmol) in THF (1 mL), with chromatography (silica gel, petroleum ether–EtOAc, 8:2, R_f = 0.40) gave **8d** (176 mg, 71%) as a clear yellowish solid; mp 100–102 °C.

IR (NaCl): 1672, 1600, 1527, 1490 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (br s, 1 H, NH), 7.55 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.38 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.20 (m, 1 H, $H4_{Ph}$), 6.04 (s, 1 H, BrClCH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.0 (C=O), 136.3 ($C1_{Ph}$), 129.2 ($C3_{Ph}$, $C5_{Ph}$), 125.6 ($C4_{Ph}$), 120.1 ($C2_{Ph}$, $C6_{Ph}$), 52.2 (BrClCH).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –259.2 (NH).

Anal. Calcd for $C_8H_7BrClNO$: C, 38.67; H, 2.84; N, 5.64. Found: C, 38.75; H, 2.90; N, 5.71.

2,2-Diiodo-*N*-phenylacetamide (8e)[11]
A 1 M LHDMS solution in THF (2 mL, 2.0 mmol, 4.0 equiv) in THF–Et_2O (3:2, 6 mL) was stirred at –78 °C for 10 min, then CH_2I_2 (0.18 mL, 589 mg, 2.2 mmol, 4.4 equiv) in THF (1.5 mL) was added dropwise to the mixture in the dark.[18c,d] After 20 min at –78 °C, phenyl isocyanate (0.06 mL, 60 mg, 0.50 mmol, 1.0 equiv) added dropwise to the mixture over 5 min. The reaction was then stirred overnight from –78 °C to r.t. The reaction was then quenched by the addition of sat. aq NH_4Cl. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Pu-

rification by flash chromatography (silica gel, petroleum ether–EtOAc, 8:2, R_f = 0.25) gave **8e** (298 mg, 77%) as a colorless solid; mp 163–165 °C.

IR (NaCl): 3081, 1671, 1602 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.32 (br s, 1 H, NH), 7.52 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.33 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.09 (m, 1 H, $H4_{Ph}$), 5.64 (s, 1 H, I_2CH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.2 (C=O), 138.0 ($C1_{Ph}$), 128.9 ($C3_{Ph}$, $C5_{Ph}$), 124.0 ($C4_{Ph}$), 119.3 ($C2_{Ph}$, $C6_{Ph}$), –33.6 (I_2CH).

^{15}N NMR (40 MHz, DMSO-d_6): δ = –260.3 (NH).

Anal. Calcd for $C_8H_7I_2NO$: C, 24.83; H, 1.82; N, 3.62. Found: C, 24.92; H, 1.86; N, 3.68.

Synthesis of Optically Active Halomethylamides

(*S*)-2-Chloro-*N*-(1-phenylethyl)acetamide [(*S*)-4d]
By following GP1, starting from (*S*)-α-methylbenzyl isocyanate (96% ee) gave (*S*)-**4d** (721 mg, 96% ee). Spectroscopic data completely match those reported for the racemate **4d**.

HPLC (column: Chiralpak IA; *n*-hexane–*i*-PrOH, 95:5; 1 mL/min, 28 °C): t_R = 8.714 min [(*R*)-enantiomer, minor], 11.194 min [(*S*)-enantiomer, major]. Racemic sample: t_R = 9.173 min [(*R*)-enantiomer], 11.219 min [(*S*)-enantiomer]. $[\alpha]_D^{20}$ –56 (*c* 2, $CHCl_3$).

(*R*)-2-Chloro-*N*-[1-(1-naphthyl)ethyl]acetamide [(*R*)-4e]
By following GP1, starting from (–)-(*R*)-1-(1-naphthyl)ethyl isocyanate (>99% ee purity) gave (*R*)-**4e** (910 mg, 97%); >99% ee. Spectroscopic data completely match those reported for the racemate **4e**.

HPLC (column: Chiralcel OD-H; *n*-hexane–*i*-PrOH, 80:20; 1 mL/min, 28 °C) t_R = 6.393 min [(*R*)-enantiomer, major], 11.586 min [(*S*)-enantiomer, minor]. Racemic sample: t_R = 6.481 min [(*R*)-enantiomer], 11.586 min [(*S*)-enantiomer]; $[\alpha]_D^{20}$ +68 (*c* 1.8, $CHCl_3$).

2-Chloro-*N*-[(1*S*)-2,3-dihydro-1*H*-inden-1-yl]acetamide [(*S*)-9a]
By following GP1, starting from (1*S*)-2,3-dihydro-1*H*-inden-1-yl isocyanate (320 mg, 2.0 mmol), ICH_2Cl (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in Et_2O gave (*S*)-**9a** (398 mg, 95%) as a white solid; >99% ee; mp 148–150 °C.

HPLC (column: Chiralpak IC; isohexane–*i*-PrOH, 95:5; 0.5 mL/min, 23 °C): t_R = 26.039 min [(*R*)-enantiomer, minor], 27.725 min [(*S*)-enantiomer, major]. Racemic sample: t_R = 26.031 min [(*R*)-enantiomer], 27.573 min [(*S*)-enantiomer]; $[\alpha]_D^{20}$ –21.4 (*c* 0.07, CH_2Cl_2).

IR (NaCl): 1655, 1590, 1472 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 1 H, $H7_{indenyl}$), 7.27 (m, 2 H, $H4_{indenyl}$, $H5_{indenyl}$), 7.25 (m, 1 H, $H6_{indenyl}$), 6.79 (br s, 1 H, NH), 5.49 (q, *J* = 7.9 Hz, 1 H, $H1_{indenyl}$), 4.12 and 4.09 (AB-system, ^2J = 15.2 Hz, 2 H, CH_2Cl), 3.02 (m, 1 H, $H3_{indenyl}$), 2.90 (m, 1 H, $H3'_{indenyl}$), 2.63 (m, 1 H, $H2_{indenyl}$), 1.86 (m, 1 H, $H2'_{indenyl}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.7 (C=O), 143.4 ($C3a_{indenyl}$), 142.2 ($C7a_{indenyl}$), 128.2 ($C5_{indenyl}$), 126.9 ($C6_{indenyl}$), 124.9 ($C4_{indenyl}$), 123.9 ($C7_{indenyl}$), 55.0 ($C1_{indenyl}$), 42.6 ($ClCH_2$), 33.8 ($C2_{indenyl}$), 30.2 ($C3_{indenyl}$).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –253.9 (NH).

Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.08; H, 5.83; N, 6.78.

2-Chloro-*N*-[(2*R*)-3-methylbutan-2-yl]acetamide [(*R*)-9b]
By following GP1, starting from (2*R*)-3-methylbutan-2-yl isocyanate (0.26 mL, 226 mg, 2.0 mmol), ICH_2Cl (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in Et_2O gave (*R*)-**9b** (298 mg, 91%) as a white solid; 99% ee; mp 42–44 °C.

Chiral GC [Varian 3800 Gas Chromatographer, CP Chiralsil-DEX CB (25 m × 0.32 mm × 0.25 mm) capillary column; 90–170 °C]: t_R = 6.359 min [(*S*)-enantiomer, minor], 6.539 min [(*R*)-enantiomer, major]. Racemic sample: t_R = 6.326 min [(*S*)-enantiomer], 6.544 min [(*R*)-enantiomer]; $[\alpha]_D^{20}$ –20.5 (*c* 1, CH_2Cl_2).

IR (NaCl): 1652, 1595, 1468, 998 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.41 (br s, 1 H, NH), 4.03 (s, 2 H, $ClCH_2$), 3.86 (m, 1 H, NHC*H*CH_3), 1.72 (m, 1 H, CH_3CHCH_3), 1.10 (d, *J* = 6.8 Hz, 3 H, NHCHCH_3), 0.902 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3), 0.898 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.0 (C=O), 50.5 (CH_3CHNH), 42.8 ($ClCH_2$), 32.8 (CH_3CHCH_3), 18.35 (CH_3CHCH_3), 18.31 (CH_3CHCH_3), 17.3 (NHCHCH_3).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –256.0 (NH).

Anal. Calcd for $C_7H_{14}ClNO$: C, 51.38; H, 8.62; N, 8.56. Found: C, 51.45; H, 8.73; N, 8.62.

***trans*-2-Chloro-*N*-(4-methylcyclohexyl)acetamide (*trans*-9c)**
By following GP1, starting from *trans*-4-methylcyclohexyl isocyanate (0.27 mL, 278 mg, 2.0 mmol), ICH_2Cl (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in Et_2O gave *trans*-**9c** (345 mg, 91%) as a white solid; 99% ee; mp 98–100 °C.

Chiral GC [Varian 3800 Gas Chromatographer, CP Chiralsil-DEX CB (25 m × 0.32 mm × 0.25 mm) capillary column; 90–170 °C]: t_R = 12.447 min (*cis*-isomer, minor), 13.027 min (*trans*-isomer, major). Racemic sample: t_R = 12.447 min (*cis*-isomer), 12.932 min (*trans*-isomer). $[\alpha]_D^{20}$ +5.9 (*c* 0.01, CH_2Cl_2).

IR (NaCl): 1661, 1475, 1421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.36 (br s, 1 H, NH), 4.00 (s, 2 H, $ClCH_2$), 3.70 (m, 1 H, $H1_{Cy}$), 1.95 (m, 2 H, $H2_{Cy}$, $H6_{Cy}$), 1.72 (m, 2 H, $H3_{Cy}$, $H5_{Cy}$), 1.33 (m, 1 H, $H4_{Cy}$), 1.18 (m, 2 H, $H2'_{Cy}$, $6'_{Cy}$), 1.04 (m, 2 H, $H3'_{Cy}$, $H5'_{Cy}$), 0.88 (d, *J* = 6.5 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.9 (C=O), 48.9 ($C1_{Cy}$), 42.7 (CH_2Cl), 33.6 ($C3_{Cy}$, $C5_{Cy}$), 32.8 ($C2_{Cy}$, $C6_{Cy}$), 31.8 ($C4_{Cy}$), 22.1 (CH_3).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –252.7 (NH).

Anal. Calcd for $C_9H_{16}ClNO$: C, 56.99; H, 8.50; N, 7.38. Found: C, 57.10; H, 8.61; N, 7.46.

2,2-Dichloro-*N*-[(1*S*)-1-phenylethyl]acetamide [(*S*)-9d]
By following GP3, starting from (1*S*)-α-methylbenzyl isocyanate (0.14 mL, 147 mg, 1.0 mmol, 96% ee) and Cl_2CH_2 (647 mg, 0.33 mL, 5.0 mmol) gave (*S*)-**9d** (199 mg, 86%) as a colorless solid; 96% ee; mp 134–136 °C.

HPLC (Chiralpak IA; isohexane–*i*-PrOH, 95:5; 0.5 mL/min, 23 °C): t_R = 13.920 min [(*S*)-enantiomer, major], 15.337 min [(*S*)-enantiomer, minor]. Racemic sample: t_R = 13.824 min [(*S*)-enantiomer], 15.338 min, [(*R*)-enantiomer]. $[\alpha]_D^{20}$ +44.5 (*c* 0.1, CH_2Cl_2).

IR (NaCl): 1659, 1593, 1470 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.33 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.30 (m, 1 H, $H4_{Ph}$), 6.73 (br s, 1 H, NH), 5.91 (s, 1 H, Cl_2CH), 5.09 (m, 1 H, NHC*H*CH_3), 1.57 (d, *J* = 6.9 Hz, 3 H, NHCHCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.2 (C=O), 141.7 ($C1_{Ph}$), 128.9 ($C3_{Ph}$, $C5_{Ph}$), 127.8 ($C4_{Ph}$), 126.0 ($C2_{Ph}$, $C6_{Ph}$), 66.4 (Cl_2CH), 49.8 (NH*C*HCH$_3$), 21.3 (NHCH*C*H$_3$).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –257.3 (NH).

Anal. Calcd for $C_{10}H_{11}Cl_2NO$: C, 51.75; H, 4.78; N, 6.03. Found: C, 51.83; H, 4.86; N 6.10.

Synthesis of Ketone 11 According to Charette's Procedure[39]

To a solution of chloroacetamide **4a** (200 mg, 1.04 mmol, 1.0 equiv) in dry CH_2Cl_2 (26 mL, concentration 0.044 M), was added 2-fluoropyridine (62 mg, 0.11 mL, 1.26 mmol, 1.1 equiv) and the resulting solution was cooled at –78 °C and stirred for 2 min. Tf_2O (354 mg, 0.21 mL, 1.26 mmol, 1.1 equiv) was added dropwise at this tem-

perature and the mixture was then stirred for 10 min. The solution was warmed at 0 °C and the reaction was stirred for 20 min. The reaction was then cooled at –78 °C and a solution of 2.0 M BnMgCl in THF (1.04 mL, 2.08 mmol, 2.0 equiv) was added dropwise over 10 min and stirred for a further 50 min. The reaction was quenched with 0.5 M HCl (8 mL) and THF (8 mL). The biphasic system was warmed at 65 °C leaving the flask open for 2 h. After extraction of the organic phase with additional CH_2Cl_2 (10 mL), the combined extracts were dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give crude **11**. Chromatography (silica gel, petroleum ether–EtOAc, 95:5) gave pure chloro ketone **11**[16a] (152 mg, 87%) as a yellow oil.

IR (NaCl): 3082, 1737, 992, 897 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 4.13 (s, 2 H), 3.91 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.1, 132.8, 129.4, 128.9, 127.5, 47.7, 46.8.

Anal. Calcd for C_9H_9ClO: C, 64.11; H, 5.38. Found: C, 64.29; H, 5.53.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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