Halogen-Imparted Reactivity in Lithium Carbenoid Mediated Homologations of Imine Surrogates: Direct Assembly of bis-Trifluoromethyl-β-Diketiminates and the Dual Role of LiCH2I

COMMUNICATION

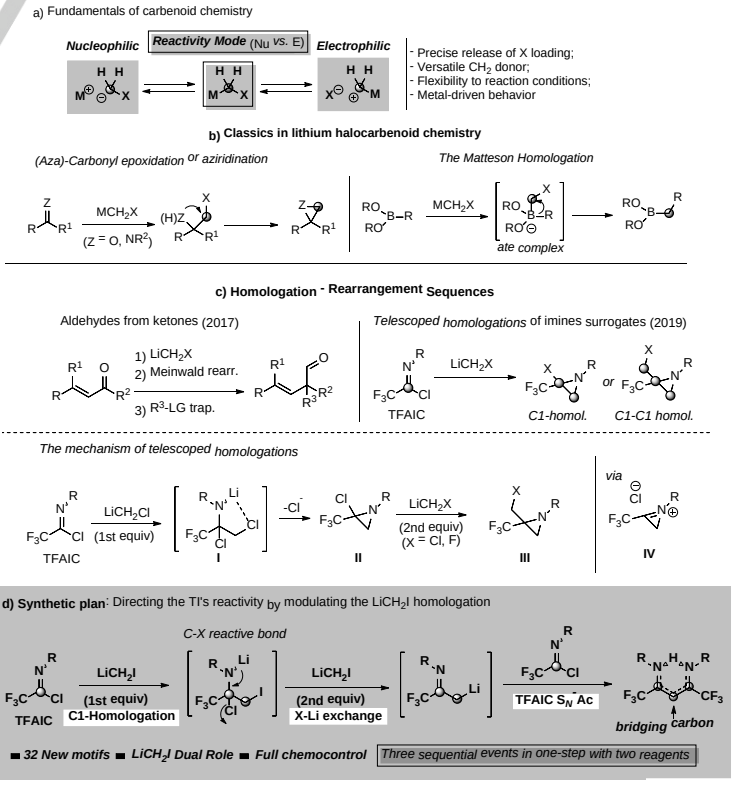
Halogen-Imparted Reactivity in Lithium Carbenoid Mediated Homologations of Imine Surrogates: Direct Assembly of bis-Trifluoromethyl-β-Diketiminates and the Dual Role of $LiCH_2I$

Dedicated to Professor José Vicente Sinisterra in the occasion of his 70th birthday

Laura Ielo,[a] Laura Castoldi,[a] Saad Touqeer,[a] Jessica Lombino,[b,c] Alexander Roller,[d] Cristina Prandi,[e] Wolfgang Holzer[a] and Vittorio Pace[a,e*]

Abstract: The selective formal insertion (homologation) of a *carbon* unit bridging the two trifluoroacetamidoyl chlorides (TFAICs) units is reported. The tactic is levered on a highly chemoselective homologation – metalation – acyl nucleophilic substitution sequence which precisely enables to assemble novel trifluoromethylated β-diketiminates within a single synthetic operation. Unlike previous homologations conducted with $LiCH_2Cl$ furnishing aziridines, herein we exploit the unique capability of iodomethyllithium to act contemporaneously as a C1 source (homologating effect) and metalating agent. The mechanistic rationale grounded on experimental evidences supports the hypothesized proposal and, the structural analysis gathers key aspects of this class of valuable ligands in catalysis.

Since their introduction in the early 1960s by Closs-Moss[1] carbenoid reagents attracted wide interest within the synthetic community for two main reasons: 1) they enable the transfer of a CH_2X fragment into a recipient carbon skeleton under nucleophilic or electrophilic regime, mainly established by the nature of the metal;[2] 2) the so-installed, *per se* reactive, C1-fragment is amenable of further derivatization within the unique operational event or, at a later stage of the sequence (Scheme 1 – *path a*).[3] This concept is beautifully illustrated in a series of benchmark transformations achieved with carbenoids and various electrophilic platforms, *e.g.* (aza)-carbonyls to oxiranes and aziridines *via* direct nucleophilic displacement (SN) of a tetrahedral intermediate (Scheme 1 – *path b*).[4] On an analogous internal SN displacement is levered the Matteson homologation of boronic esters,[5] a powerful and highly versatile reaction used recently by Aggarwal to introduce the assembly line synthesis concept.[6] In general, these classics in carbenoid-mediated chemistry deliver the *expected* homologated arrays or thereof derivatives.[7] The high reactivity of tetrahedral intermediates formed upon the addition of a carbenoid can be advantageously exploited for triggering molecular rearrangements, conducting to complex architectures within a single synthetic operation (Scheme 1 – *path c*).[8] In this context, our group reported in 2017 a carbenoid homologation - Meinwald rearrangement – α-functionalization approach directly converting vinyl ketones into homologated α-fully substituted aldehydes.[8a] Notably, the nature of the halogen (Cl, Br, I) did not influence the outcome of the process. Later in 2019, we introduced the concept of telescoped homologation of imine surrogates for accessing – *via* trivial stoichiometric control – mono- or di-homologated CF_3-aziridines starting from trifluoromethylated imine surrogates (trifluoroacetimidoyl chlorides, TFAICs).[8b, 9] The hypothesized reaction mechanism based on the experimental evidence points out that after the first homologation event conducting to tetrahedral intermediate (TI) **I**, a selective cyclization of the lithium amide on the installed chloromethyl-fragment took place, giving the mono-homologated α-chloro-aziridine (**II**).[8b] In case of excess of the reagent (not necessarily $LiCH_2Cl$), the double C1-C1 homologation product (**III**) is obtained *via in situ* spontaneous formation of an electrophilic azirinium ion (**IV**).[10] The depicted scenario clearly documents the crucial role displayed by the intermediate **I** and, we reasoned that modulating the homologation phase inserting a distinct halomethyl fragment - potentially susceptible of further manipulation - could constitute a tactic for enabling the formal insertion of a *carbon* conjunctive of two TFAIC units (Scheme 1 – *path d*).



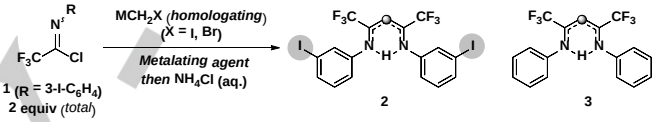
[*] [a] University of Vienna, Department of Pharmaceutical Chemistry - Althanstrasse, 14 A-1090, Vienna, Austria. E-mail: vittorio.pace@univie.ac.at Web: http://drugsynthesis.univie.ac.at/; [b] Fondazione Ri.MED - Via Bandiera 11, 90133 Palermo, Italy; [c] University of Palermo, Department STEBICEF - Via Archirafi 32, 90123 Palermo, Italy; [d] University of Vienna, X-Ray Structure Analysis Center - Waehringerstrasse 42 A-1090 Vienna, Austria; [e] University of Turin, Department of Chemistry - Via P. Giuria 7, 10125 Turin, Italy.

Scheme 1. General context of the presented work.

Collectively, our homologative synthetic plan could be regarded as a tool for bridging two carbon centers with a connecting C1-unit. Herein, we document the concept of chemoselective homologation of TFAIC mediated by $LiCH_2I$. We anticipate the dual (unprecedented) role displayed by the iodocarbenoid: it delivers the C1 synthon (homologating effect) and, accomplishes the critical metalation thus, forming a α-iminomethyl lithium species which attacks the second TFAIC unit, finally yielding the products. Our strategy would enable a smooth access to fluorinated β-diketiminates a significantly challenging class of ligands for which a modular and highly efficient synthetic method is still underdeveloped.[11] Interestingly, non-fluorinated analogues (often called *NacNac* in analogy to more common *acac* ligands)[12] emerged recently as versatile ligands (σ-donors) for stabilizing low-coordinate Fe species[13] and Ir-photoreductants.[14]

The iodo-containing TFAIC (**1**) was selected as the model substrate because of gathering information on the chemoselectivity of a potentially concomitant aryl iodine-metal exchange (Table 1). Being the expected adduct the homologated product of two TFAIC building blocks, 2 equiv of them were required *per* each CH_2 unit supplied. Installing the CH_2I unit (*via* treatment with CH_2I_2 / MeLi-LiBr),[15] followed by iodo-metal exchange with MeLi-LiBr provided a 76:24 ratio mixture of homologated compounds **2** and **3** (entry 1). Using LiBr-free MeLi as the metalating agent, resulted in increasing the formation of **3** (55:45 ratio) because of facilitated Ar-I / Li exchange (entry 2), thus suggesting the presence of LiBr as optimal for the reaction. Generating $LiCH_2I$ with *n*-BuLi-LiBr benefited the formation of **2** (entry 3), though the addition of the facilitating lithiating ligand TMEDA inverted the ratio in favour of **3** (entry 4). Switching to other common organolithiums (*s*-BuLi-LiBr and *t*-BuLi-LiBr) had little effect on the reaction outcome (entries 5-6) while, bromomethyllithium ($LiCH_2Br$,[16] generated from $BrCH_2I$ and MeLi-LiBr) could be used as a competent C1-unit donor (entry 7), giving **2** in slightly lower yield. Pleasingly, these experimental evidences – *i.e.* different homologating behaviour of both $LiCH_2I$ and $LiCH_2Br$ compared with $LiCH_2Cl$ reported before - fully support the hypothesized logic harnessed on rendering further reactive the TI. Increasing the loading of both reactants $LiCH_2I$ and MeLi-LiBr improved both the **2**:**3** ratio and the isolated yield of **2**, though a considerable excess did not further boost the transformation (entries 8-9). A significant solvent dependence was noticed using diethyl ether and toluene (entries 10-11) in place of THF. A remarkable improvement was achieved when using the same $LiCH_2I$ as C1 source (*homologating role*) and as I/Li exchange agent (*metalating role*).[17] This unprecedented double effect of the carbenoid reagent was subjected to further investigation to maximize both ratio and conversion (*vide infra* for mechanistic details). Cognizant that – constitutively - the existence time of a carbenoid is very limited[18] and, its productive employment requires the adoption of Barbier-type conditions at -78 °C, a careful optimization of the carbenoid loading was secured. Using 1.8 equiv of $LiCH_2I$ in each of the steps gave a 93:7 **2**:**3** ratio at 87% conversion (entry 12), whereas a slight excess during the homologation (entry 13) was slightly detrimental compared to inverting the excess in favour of the metalation step (entries 13-14). We found highly beneficial adding the TFAIC portionwise: at the beginning of the reaction only 1 equiv was present to ensure the formation of the TI, thus leaving the second portion to be added just after the metalation event. Under these conditions, the desired compound **2** was obtained in an excellent 91% isolated yield (entry 15). Some practical aspects of the transformation merit mention: 1) the CH_2I_2 precursor of the carbenoid was added in one-pot at the beginning of the reaction because its transformation into $LiCH_2I$ requires *minimum* a stoichiometric amount of MeLi-LiBr; 2) this implicitly accounts that the unreacted CH_2I_2 remains in *reservoir* mode before the addition of the second aliquot of MeLi-LiBr for the metalating phase; 3) an optimal time of 5 min between the end of the addition of MeLi-LiBr (for forming the homologating $LiCH_2I$) and, the starting of the second addition of the same MeLi-LiBr (for forming the metalating $LiCH_2I$) benefited the process; 4) varying the temperatures for one or both steps was detrimental for the reaction, giving complex mixtures (data non shown).

Table 1. Reaction optimization.

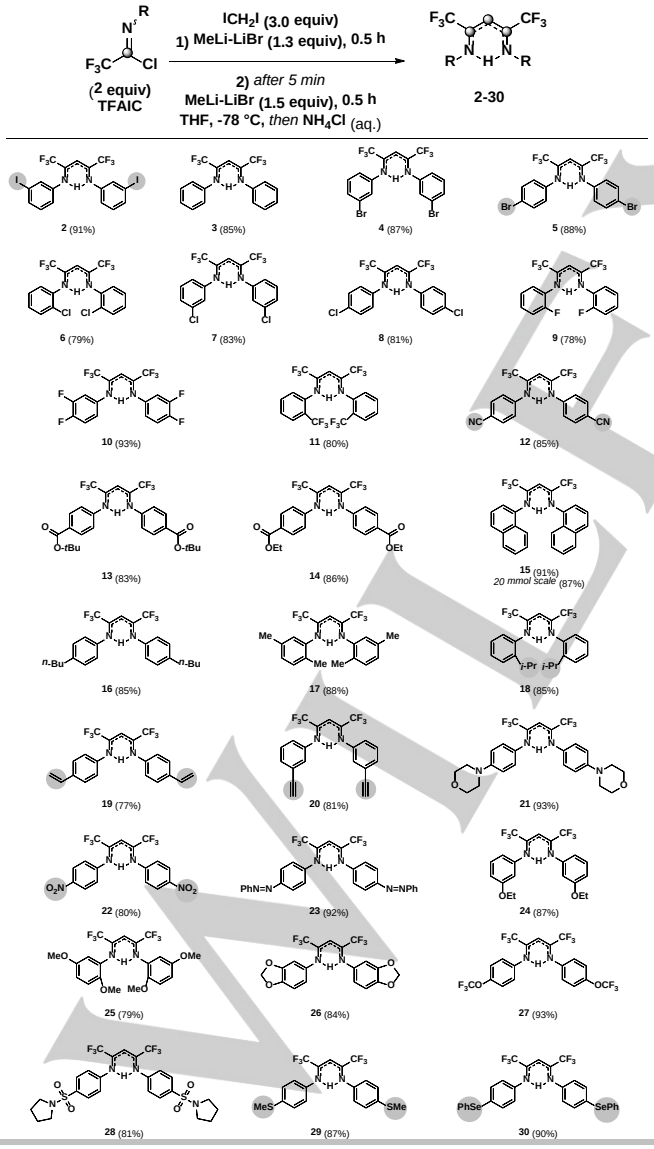


Entry	Homologating agent (equiv)[a]	Metalating agent (equiv)	Conversion[b]	Ratio **2** / **3**	Yield of **2** (%)[c]
1	$LiCH_2I$ (1.2)	MeLi-LiBr (1.2)	41	76:24	26
2	$LiCH_2I$ (1.2)	MeLi (1.2)	36	55:45	14
3	$LiCH_2I$ (1.2)	*n*-BuLi-LiBr (1.2)	39	68:32	22
4[d]	$LiCH_2I$ (1.2)	*n*-BuLi-LiBr (1.2)	35	41:59	11
5	$LiCH_2I$ (1.2)	*s*-BuLi-LiBr (1.2)	31	63:37	15
6	$LiCH_2I$ (1.2)	*t*-BuLi-LiBr (1.2)	36	72:29	23
7	$LiCH_2Br$ (1.2)	MeLi-LiBr (1.2)	33	70:30	19
8	$LiCH_2I$ (1.8)	MeLi-LiBr (1.8)	72	81:19	54
9	$LiCH_2I$ (2.3)	MeLi-LiBr (2.3)	74	80:20	55
10[e]	$LiCH_2I$ (1.8)	MeLi-LiBr (1.8)	18	83:17	10
11[f]	$LiCH_2I$ (1.8)	MeLi-LiBr (1.8)	27	79:21	16
12	$LiCH_2I$ (1.8)	$LiCH_2I$ (1.8)	87	93:7	76
13	$LiCH_2I$ (1.8)	$LiCH_2I$ (1.3)	83	90:10	70
14	$LiCH_2I$ (1.3)	$LiCH_2I$ (1.8)	89	98:2	83
15	$LiCH_2I$ (1.3)	$LiCH_2I$ (1.5)	95	>99:1	91

[a] Unless stated otherwise (entries 2-6), $LiCH_2I$ was generated under Barbier conditions in THF starting from CH_2I_2 and MeLi-LIBr at -78 °C for 1 h. The metalating agent was added after 5 min from the end of the homologation step. [b] The ratio has been calculated by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as internal standard. [c] Isolated yield. [d] TMEDA (1.2 equiv) was added. [e] Reaction run in Et_2O. [f] Reaction run in toluene.

Having set the optimal conditions for the transformation, we next studied the scope (Scheme 2). Confirming the chemoselective profile of the method, different halogen substituted TFAICs were amenable substrates for the methodology. Regardless the position on the aromatic ring (*ortho*, meta, *para*), also the potentially exchangeable bromo analogues reacted in high yield giving the homologated substrates **4** and **5**. An analogous outcome was observed when chlorinated (**6**-**8**), monofluoro (**9**),

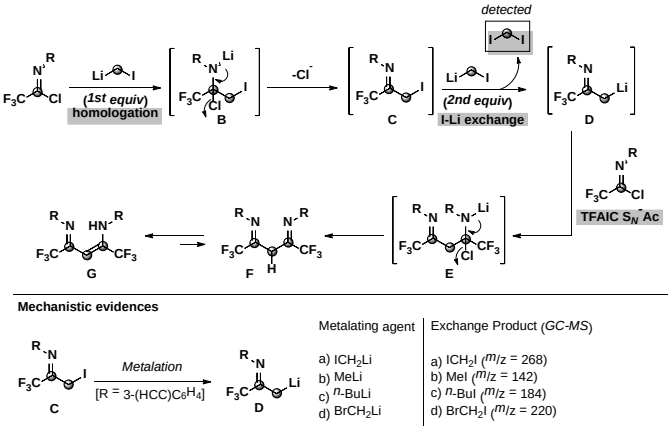
difluoro (**10**) or trifluoromethyl (**11**) TFAICs derivatives were employed. Genuine chemoselectivity was deducted when multi-electrophilic TFAICs were tested, thus demonstrating the chemical integrity of nitrile (**12**) and esters [*t*-Bu (**13**) and Et (**14**)]. The reaction of the naphthyl-derivative was crucial for obtaining the analogue (**15**) whose X-ray analysis gave fundamental details on the structure of these new synthesized motifs (*vide infra*). Notably, scaling-up the preparation of **15** at 20 mmol scale was possible in comparable yield. Decorating the starting TFAICs with aliphatic residues of variable steric hindrance [4-*n*-Bu (**16**), 2,5-di-Me (**17**) and *i*-Pr (**18**)] did not alter the efficiency of the technique. The potentially cyclopropyl-manifold vinyl motif (**19**) remained untouched during the whole sequence, as well as, the terminal alkyne (**20**) - amenable of deprotonation under the basic conditions required. Introducing nitrogen-centered functionalities was permitted, as observed in the case of the morpholino- (**21**), nitro- (**22**) and diazo- (**23**) containing substrates. Incorporating electron-donating groups such as ethers [3-ethoxy- (**24**), 2,5-dimethoxy- (**25**)], cyclic acetal [1,3-benzodioxolane (**26**)] and fluorinated ether [4-trifluoromethoxy- (**27**)] further extended the scope of the method.



Scheme 2. Scope of the reaction for preparing bis-CF_3-β-diketiminates.

TFAICs presenting sulfur substituents reacted equally well, yielding the 4-sulfonamido- (**28**) and 4-thiomethyl (**29**) analogues. Interestingly, the 4-phenylseleno- substituted TFAIC did not undergo any concomitant Se/Li exchange,[19] furnishing the desired compound (**30**) in 90% yield. We consider these findings highly relevant for establishing a robust and flexible route towards bis-CF_3-β-diketiminates with vistas to their high-throughput screening in catalysis.

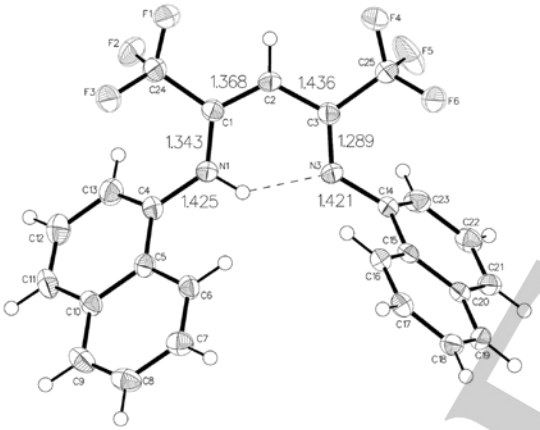
Mechanistically, the nucleophilic addition of $LiCH_2I$ to TFAIC (**A**) results in the formation of a tetrahedral intermediate (**B**), which through the elimination of a chloride ion, conducts to the α-iodomethylimine (**C**). As a consequence of the tamed electrophilicity of the azacarbonyl carbon (compared to the starting TFAIC) of this non isolable species, the subsequent addition of the organolithium reagent furnishes the α-iminomethyl lithium (**D**). This nucleophilic fragment reacts with the second TFAIC building block according to an analogous addition-elimination pathway (**E**), yielding the homologated adduct (**F**). Finally, the intervention of a tautomeric equilibrium delivers the compound in the observed form **G**. The plausibility of the prospected mechanism is grounded on the following experimental evidences: 1) the GC-MS analysis of the reaction crude indicates the presence of CH_2I_2 at the end of the reaction, indicating that although a part of it has been consumed for providing the C1 homologating unit, it is re-formed after the metalating step; 2) when the metalation was conducted with MeLi, *n*-BuLi and $LiCH_2Br$ (entries 2, 3, 7 - Table 1), the GC-MS analysis of the crude showed the peaks of MeI, *n*-BuI and $BrCH_2I$ diagnostic for the metalating mechanism suggested; 3) additionally, the relatively highly boiling *n*-BuI (bp 130 °C) could be recovered and unambiguously elucidated after chromatography on silica gel of the reaction crude. Collectively, in the optimized reaction only 1 equiv of CH_2I_2 (of the 3.0 equiv initially present) is used for the transformation, being at least 2.0 equiv regenerated during the metalating step.



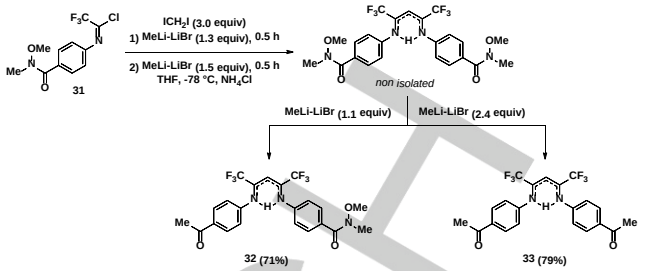
Scheme 3. Mechanistic rationale and proof of the metalating capability of $LiCH_2I$.

The X-ray analysis of compound **15** shows interesting characteristics of the β-diketiminate skeleton, being firstly evident the asymmetry of the conjugated planar system. The two TFAIC units connected to the homologating element are not equal: the bond lengths of N1-C1 (1.343 Å) and N3-C3 (1.289 Å) are different and they are intermediate between an average sp^2 N-C (1.280 Å) and an average sp^3 N-C (1.460 Å).[20] The β-diketiminate array is also featured by a hydrogen atom attached to N1 placed at H-bond distance with N3, thus forming the N1-H-N3 angle of 136.94°. Bond lengths of C1-C2 (1.368 Å) and C2-C3 (1.436 Å) – again not equal – fully supports the partial double bond character of these elements [*cfr.* average sp^3 C-C (1.540 Å), average sp^2 C-C (1.340 Å)].[20] Merged together, this information are consistent with an extended conjugation across the central motif (N1-C1-C2-C3-N3) with the final result of rendering it almost planar, as a consequence of the small torsion angles (N1-C1-C2-C3, 2.65 °) and (N3-C3-C2-C1, 6.95 °), respectively.

Figure 1. X-ray structural analysis of compound **15** (CCDC 2007131).



Spurred by the highly chemoselective profile observed in the reaction with esters (**13**-**14**, Scheme 2), we wondered if installing a Weinreb amide (*per se* less reactive than esters)[21] on the TFAIC would have allowed to realize sequential additions of different organometallics in order to rapidly diversify – without isolating - the flexible β-diketiminate backbone (Scheme 4). This scaffold - featuring the two electrophilic Weinreb amide appendixes - upon immediate treatment with the nucleophile (MeLi-LiBr) was amenable of selective *mono*- or *di*-functionalization *via* trivial control of stoichiometry, giving **32** and **33**, respectively. Despite the constitutional acidity of the N-H proton no basic (*i.e.* deprotonating) effect was noticed when using MeLi-LiBr as the nucleophile thus, highlighting the exceptional chemoselective acylating capability of Weinreb amides.



Scheme 4. Consecutive homologation-diversification of a Weinreb amide decorated TFAIC.

In summary, we have documented the formal insertion of a carbon atom between two TFAICs arrays, resulting in the one-step assembly of the novel bis-trifluomethylated β-diketiminate backbone. The strategy relies on the stoichiometry controlled homologation of one TFAIC unit with the nucleophilic carbenoid iodomethyllithium acting contemporaneously as a C1 (homologating) and metalating (of the intermediate α-iodomethylimine) agent. The fine tuning of the reaction conditions guarantees a high level of chemocontrol as deducted from the substrate scope underlining the tolerance for functionalities whose chemical integrity could enable late-stage derivatization. The structural analysis diagnostic for an extended planar conjugate system secured insights valuable for further designing and developing new applications of these ligands in synthetic chemistry.

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Keywords: Homologation • Metalation • Carbenoids • Imines • Chemoselectivity.

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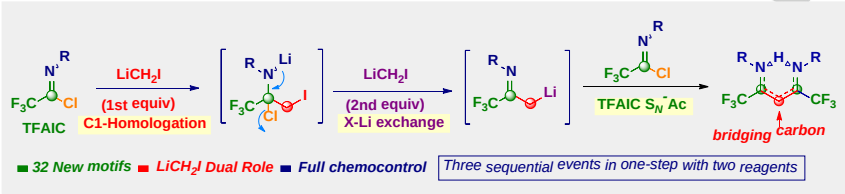

*Laura Ielo, Laura Castoldi, Saad Touqeer, Jessica Lombino, Alexander Roller, Cristina Prandi, Wolfgang Holzer and Vittorio Pace**

Halogen-Imparted Reactivity in Lithium Carbenoid Mediated Homologations of Imine Surrogates: Direct Assembly of bis-Trifluoromethyl-β-Diketiminates and the Dual Role of $LiCH_2I$

The treatment of a trifluoroacetimidoyl chloride (TFAIC) with the carbenoid iodomethyllithium results in the chemoselective formation of a bis-trifluoromethyl-β-diketiminate. This sequential two-events strategy involves the homologation of the imine surrogate followed by the lithiation of the intermediate operated by the same carbenoid and attack of a second TFAIC unit.