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Highly Selective Preparation of Allenic and Homopropargylic Hydrazides through Regiospecific Addition of Propargyltrichlorosilane and Allenyltrichlorosilane to Various Types of *N*-Acylhydrazones

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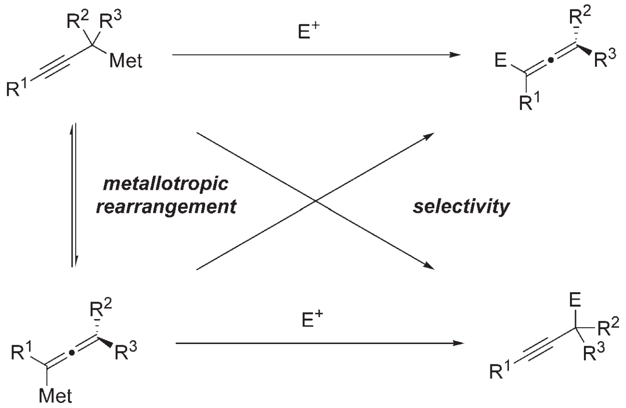
Abstract: The highly selective preparation of various types of allenic and homopropargylic hydrazides through regiospecific allenylation and propargylation of the corresponding *N*-acylhydrazones is reported. These carbon-carbon bond-forming reactions employing *in situ* prepared propargyl- and allenyltrichlorosilanes proceed smoothly in *N*,*N*-dimethylformamide (DMF) without any metal catalysis (neutral Lewis base activation of nucleophiles). The use of Hünig's base as an additive is beneficial in terms of chemical yields.

Keywords: alkynes; allenes; C–C bond formation; copper; hydrazones; nickel; silanes

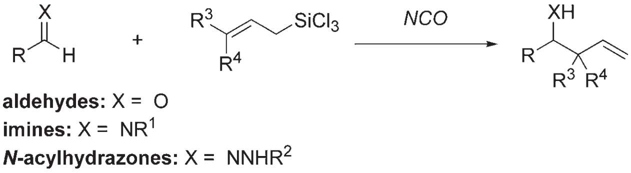


Scheme 1. Metallotropic rearrangement and non-regiospecific nucleophilic addition.

Functionalized nitrogen-containing allenes and alkynes such as allenic[1] and homopropargylic[2] amines or hydrazines have proved to be highly versatile intermediates and building blocks in modern organic synthesis.[3] Among the most efficient routes to these types of compounds are carbon-carbon bond-forming reactions such as regiospecific addition of propargyl- and allenyl-metal compounds to C=N electrophiles.[3,4] However, the main drawback concerning the use of propargyl- and allenyl-metal derivatives is the potential formation of product mixtures due to metallotropic rearrangement[5] between these species prior to the reaction and/or non-regiospecific addition to electrophiles (Scheme 1).[6]

Additionally, accessibility to these propargyl and allenyl nucleophiles is highly substrate-dependent.[5–7] Furthermore, the use of organometallic nucleophiles or metal catalysts, especially for large-scale synthesis, is sometimes undesirable with respect to safety and environmental considerations.[8] In this context, we recently reported that neutral (non-ionic) Lewis bases such as *N*,*N*-dimethylformamide (DMF), hexamethylphosphoramide (HMPA), sulfoxides or phosphine oxides promote nucleophilic additions of allyl- and crotyltrichlorosilanes to aldehydes,[9] imines[10] and *N*-acylhydrazones (Scheme 2).[11,12] All these reactions proceeded without using any metal catalysts since these non-ionic Lewis bases, which are defined as *n*eutral *c*oordinate-*o*rganocatalysts (*NCO*s),[13] could activate the trichlorosilyl nucleophiles by coordination to the Lewis acidic silicon atom.

Various other catalytic systems have been developed for allylation of *N*-acylhydrazones[14] and imines.[15] On the other hand, several methods have been reported



Scheme 2. *NCO*-mediated allylations and crotylations of aldehydes, imines and *N*-acylhydrazones.

for propargylation and/or allenylation of aldehydes.[16] However, to the best of our knowledge to date only three examples for the propargylation and/or allenylation of C=N electrophiles are known. Goré et al. realized the allenylation of achiral and chiral hydrazones with 1-methoxyallenyllithium in diethyl ether.[1b,17] Akiyama and co-workers reported the enantioselective allenylation and propargylation of an α-imino ester with propargyl- and allenyltin reagents respectively, catalyzed by a Cu(I) complex of a chiral binap derivative.[18] Prajapati et al. described the propargylation of aromatic *N*-arylimines, *N*-arylnitrones and *N*-phenylhydrazones *via* an indium-promoted Barbier-type reaction using propargyl bromide.[19] However, in all cases substrate scope, selectivities and yields were rather limited and stoichiometric amounts of metal derivatives were required.

Previously, we reported selective *in situ* preparation of both propargyltrichlorosilanes and allenyltrichlorosilanes starting from the same propargylic halides, followed by addition to several aldehydes in order to form the corresponding allenic and homopropargylic alcohols, respectively (Scheme 3).[20] More recently, we have improved this transformation significantly with respect to selectivities, yields and substrate scope (Scheme 3).[21]

Remarkably, these allenylation and propargylation reactions proceeded regiospecifically without metal catalysis. DMF might coordinate to the silicon atom of propargyltrichlorosilane and allenyltrichlorosilane resulting in the formation of highly reactive hypervalent silicon species, which in turn smoothly add to aldehydes *via* assumed cyclic transition states **A** and **B** (Figure 1).

Based on this background, we decided to develop the selective allenylation and propargylation of C=N electrophiles with propargyltrichlorosilane and allenyltrichlorosilane for the synthesis of allenic and homopropargylic amines and hydrazines, respectively (Scheme 3). We selected *N*-acylhydrazones as imine surrogates because of their stability compared to the corresponding imines. These substrates can be easily prepared and purified, they are crystalline and can be stored for several months at room temperature without decomposition. We assumed that in these supposed S_E2' type additions similar reaction intermediates might be formed employing *N*-acylhydrazones instead of aldehydes as electrophiles. The corresponding cyclic transition states **C** and **D** are represented in Figure 1.

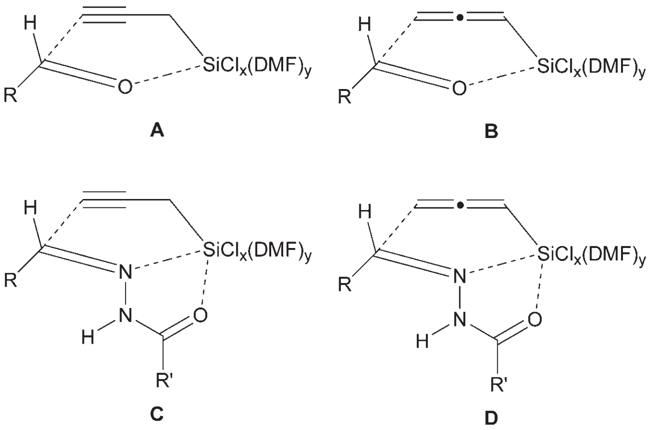
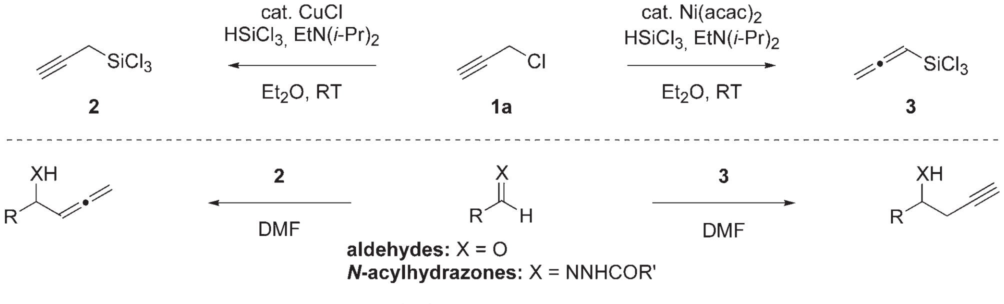


Figure 1. Supposed cyclic transition states **A** and **B** or **C** and **D** for selective allenylations and propargylations of aldehydes or *N*-acylhydrazones, respectively.

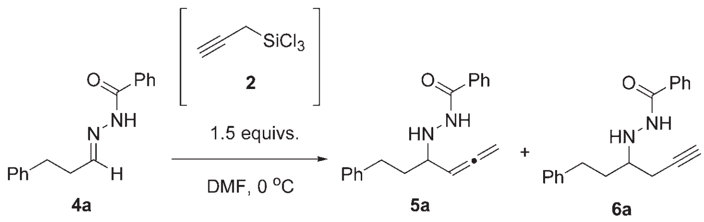
First, we examined the conditions for the reaction between propargyltrichlorosilane (**2**) and the *N*-benzoylhydrazone derivative of 3-phenylpropanal (**4a**) as model substrates (Table 1). Propargyltrichlorosilane (**2**) was prepared *via* silylation of propargyl chloride (**1a**; 2.0 equivs.) by using Hünig's base (4.0 equivs.) and trichlorosilane (4.4 equivs.) in dry ether in the presence of anhydrous copper(I) chloride (5 mol %), as described before.[21] The ethereal solution of *in situ* prepared nucleophile **2** (~ 1.5 equivs. based on NMR yield) was then added to a solution of substrate **4a** (1.0 equiv.) in dry DMF at 0 °C.

Initial experiments revealed the importance of the amount of DMF and the reaction time, even though the best yield for the desired product **5a** was moderate (Table 1, entries 1 and 2). Further optimization of the *in situ* formation of nucleophile **2** showed that the use of propargyl bromide (**1b**) instead of propargyl chloride (**1a**) significantly accelerated the silylation while conserving the excellent selectivities.[22] Additionally, extensive metal screening revealed the beneficial replace-



Scheme 3. Selective silylation of propargyl chloride (**1a**) and DMF-mediated propargylations and allenylations of aldehydes and/or *N*-acylhydrazones with trichlorosilanes **2** and **3**.

Table 1. DMF-mediated allenylation of model substrate **4a** with *in situ* prepared propargyltrichlorosilane (**2**).



Entry	DMF [M][a]	Time [h]	Yield [%]	Ratio[b] **5a** : **6a**
1[c]	0.5	6	36	>99:1
2[c]	0.25	12	65	>99:1
3[d]	0.25	12	75	>99:1
4[d]	0.1	12	82	>99:1
5[d]	0.25	24	88	>99:1
6[d]	0.1	24	93	>99:1
7[d]	0.1	60	95	>99:1

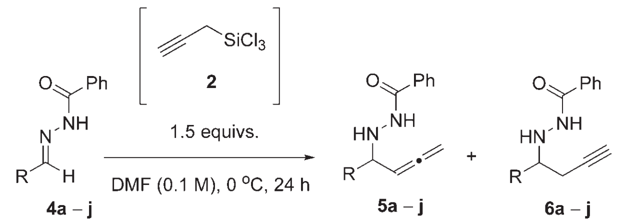
[a] Concentration of substrate **4a** in DMF.

[b] Determined by ^{1}H NMR analysis of the isolated material.

[c] Propargyltrichlorosilane (**2**) was prepared from propargyl chloride (**1a**) in the presence of copper(I) chloride.

[d] Propargyltrichlorosilane (**2**) was prepared from propargyl bromide (**1b**) in the presence of copper(II) fluoride.

Table 2. DMF-mediated allenylation of various types of *N*-acylhydrazones **4** with *in situ* prepared propargyltrichlorosilane (**2**).



Entry	Substrate **4**: R	Yield [%]	Ratio[a] **5**:**6**
1	**4a**: $PhCH_2CH_2$	93	>99:1
2	**4b**: Ph	85	99:1
3	**4c**: 4-ClC_6H_4	83	99:1
4	**4d**: 4-$MeOC_6H_4$	65	98:2
5	**4e**: (*E*)-PhCH=CH	80	>99:1
6	**4f**: *n*-Pr	80	>99:1
7	**4g**: *i*-Pr	76	>99:1
8	**4h**: Cy	70	>99:1
9	**4i**: *t*-Bu	68	>99:1
10	**4j**: CO_2Et	87	>99:1

[a] Determined by ^{1}H NMR analysis of the isolated material.

ment of copper(I) chloride by copper(II) fluoride. The combined use of propargyl bromide and copper(II) fluoride was therefore used for the *in situ* preparation of **2** in view of allenylation reactions (entries 3–7). Thus, yields for the allenylation of substrate **4a** were improved to 75% (12 h; entry 3 *vs.* entry 2) and 88% (24 h; entry 5), respectively. Finally, conducting the allenylation reaction in DMF (0.1 M) gave the best results with yields up to 95% (60 h; entry 7) and exclusive formation of compound **5a**.

This improvement might be attributed to both a more homogeneous reaction mixture and more efficient activation of nucleophile **2** by the neutral Lewis base DMF.

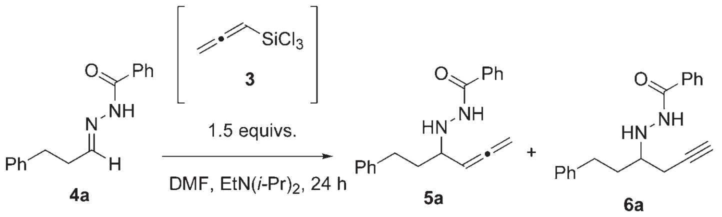
Next, we extended the optimized allenylation conditions to the use of various types of *N*-acylhydrazones in order to examine scope and limitations of our procedure (Table 2). We were delighted to find that our optimized reaction conditions were tolerated by a wide range of *N*-acylhydrazones. Aromatic hydrazones **4b** and **4c** as well as α-hydrazono ester **4j** proved to be excellent substrates, with yields between 83% and 87% and excellent selectivities (Table 2, entries 2, 3 and 10). Aliphatic substrates **4f**–**h** and α,β-unsaturated hydrazone **4e** also reacted smoothly and with complete regiospecificity to form the corresponding allenic hydrazides **5** (70–80% yield; entries 5–8). On the other hand, aromatic substrate **4d** and the sterically demanding aliphatic hydrazone **4i** gave slightly lower yields (entries 4 and 9). It is noted that in almost all cases allenylations proceeded with complete regiospecificity; only in the case of aromatic hydrazones **4b**–**d** were very small amounts of the corresponding homopropargylic products **6** detected (entries 2–4).

We then studied the reaction conditions for propargylation of model substrate **4a** by using allenyltrichlorosilane (**3**; Table 3). Allenyltrichlorosilane (**3**) was prepared through silylation of propargyl chloride (**1a**; 2.0 equivs.) or propargyl bromide (**1b**; 2.0 equivs.)[22] by using Hünig's base (4.0 equivs.) and trichlorosilane (4.4 equivs.) in dry ether in the presence of anhydrous bis(2,4-pentanedionato)nickel(II) (5 mol %), as described before.[21] The ethereal solution of *in situ* prepared nucleophile **3** (~1.5 equivs.) was then added to a solution of substrate **4a** (1.0 equiv.) in dry DMF at 0 °C. As was the case in the allenylation study (cf. Table 1), results were highly dependent on the amount of DMF (Table 3; entries 1, 2 and 4). The use of a large excess of nucleophile **3** did not improve the yield (entry 3), whereas the addition of five equivalents of Hünig's base gave the best result at 0 °C (75% yield; entry 5).

In addition, reactions at 10 °C proved to be accelerated and gave better results than reactions at 0 °C (entries 6 and 8 *vs.* entries 2 and 5, respectively). Interestingly, doubling the amount of nucleophile **3** only slightly increased the yield of the desired product **6a** (entry 7 *vs.* entry 6). On the other hand, it was possible to decrease the amount of Hünig's base to 1.5 equivalents without loss of yield and selectivity (entry 11).

This improvement in the presence of Hünig's base might be attributed to the Brønsted base activation of electrophile **4a** *via* N–H deprotonation to form species **E**,[23] followed by *in situ* tethering of nucleophile **3** to

Table 3. DMF-mediated propargylation of model substrate **4a** with *in situ* prepared allenyltrichlorosilane (**3**).



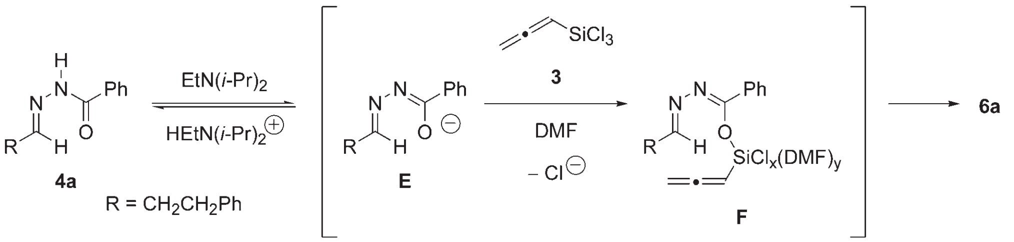
Entry	**3** [equivs.]	DMF [M][a]	Temp. [°C]	EtN(*i*-Pr)$_2$ [equivs.]	Yield [%]	Ratio[b] **5a**:**6a**
1[c]	1.5	0.5	0	–	35	1:>99
2[d]	1.5	0.1	0	–	65–68	1:>99
3[d]	6.0	0.1	0	–	49	1:>99
4[d]	1.5	0.2	0	–	55	1:>99
5[d]	1.5	0.1	0	5.0	75	1:>99
6[d]	1.5	0.1	10	–	75	1:>99
7[d]	3.0	0.1	10	–	79	1:>99
8[d]	1.5	0.1	10	5.0	86	1:>99
9[d]	1.5	0.1	10	10.0	88	1:>99
10[d]	1.5	0.1	10	3.0	85	1:>99
11[d]	1.5	0.1	10	1.5	85	1:>99
12[d]	1.5	0.1	10	1.0	80	1:>99
13[d]	1.5	0.1	10	0.5	70	1:>99

[a] Concentration of substrate **4a** in DMF.
[b] Determined by ^{1}H NMR analysis of the isolated material.
[c] Allenyltrichlorosilane (**3**) was prepared from propargyl chloride (**1a**).
[d] Allenyltrichlorosilane (**3**) was prepared from propargyl bromide (**1b**).

generate intermediate **F** (Si–O bond formation; Scheme 4).[24]

The C–C bond formation would then proceed through *intramolecular* nucleophilic addition of the oxygen-bound allenylsilane (neutral Lewis base activation by DMF-coordination to the silicon atom) to the C=N double bond (formation of product **6a**). This proposed mechanism could be considered as a form of dual activation,[25] since electrophile and nucleophile might be activated by a Brønsted base and a neutral Lewis base (*NCO*), respectively. Other plausible explanations for the significantly improved chemical yields include the Lewis base activation of nucleophile **3** by Hünig's base or its neutralizing effect on the potentially acidic reaction medium or the improved solubility of reaction intermediates.

In order to elucidate the beneficial role of Hünig's base, several control experiments were carried out. *In situ* prepared allenyltrichlorosilane (**3**) was purified by distillation under reduced pressure (ratio **2**:**3**=1:>99)[26] and used instead of *in situ* prepared **3** for the propargylation of model hydrazone **4a** (under otherwise identical conditions). The reaction proceeded smoothly at 10 °C to afford the desired product **6a** in comparable yield (70% *vs.* 75%) with complete regiospecificity. When the same reaction was carried out in the presence of Hünig's base (1.5 equivs.) the isolated yield was also significantly higher (82%), as was the yield observed for the use of *in situ* prepared **3** (85%). Both experiments confirm that a small amount of the nickel salt (potentially present in the supernatant of the *in situ* preparation of **3**) does not affect the reaction outcome and

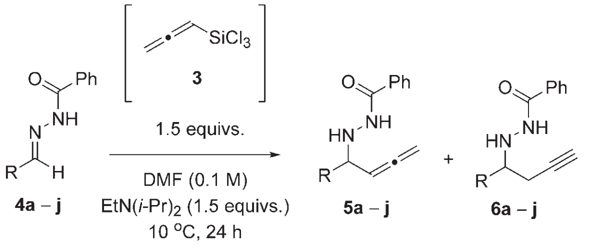


Scheme 4. N–H Deprotonation of electrophile **4a** with Hünig's base, followed by *in situ* tethering of nucleophile **3** and supposed *intramolecular* DMF-mediated C–C bond formation to form the desired product **6a**.

that Hünig's base is also efficient when distilled **3** is used. Moreover, when the propargylation was performed with Hünig's base instead of DMF as a solvent, under otherwise identical conditions, no reaction occurred ($<5\%$ yield). This result underlines the crucial role of DMF as an *NCO* (neutral Lewis base activation) and excludes that Hünig's base might activate nucleophile **3** in a Lewis basic fashion. In this context, it is also important to mention that similar results were obtained in a series of experiments using distilled propargyltrichlorosilane (**2**; ratio **2**:**3** = ~80:20)[26] instead of *in situ* prepared **2**.[27] These experiments show that under the conditions employed: (1) metal salts do not influence the course of allenylation and propargylation, (2) Hünig's base is an effective activator, but does not serve as a Lewis base in these reactions, and (3) Hünig's base might activate the corresponding electrophile **4** in a Brønsted basic manner (Scheme 4), even though simple neutralization or solubility effects cannot be excluded. Further mechanistic studies are in progress.

Next, we tested the substrate scope under the optimized propargylation conditions (Table 4). We were pleased to see that selective propargylation of various hydrazones **4** proceeded with **3**, even though yields were slightly decreased compared to those obtained using **2**. Again, aromatic hydrazones **4b** and **4c** together with α,β-unsaturated substrate **4e** and α-hydrazono ester **4j** were the best substrates, the corresponding homopropargylic hydrazides **6** were obtained in 70–76% yield with excellent selectivities (Table 4, entries 2, 3, 5 and 10). All aliphatic substrates **4f**–**i** reacted smoothly with nucleophile **3** to form the desired products **6f**–**i** exclusively (58–69% yield; entries 6–9).

Table 4. DMF-mediated propargylation of various types of *N*-acylhydrazones **4** with *in situ* prepared allenyltrichlorosilane (**3**).



Entry	Substrate **4**: R	Yield [%]	Ratio[a] **5**:**6**
1	**4a**: $PhCH_2CH_2$	85	1:> 99
2	**4b**: Ph	72	1:99
3	**4c**: 4-ClC_6H_4	70	1:99
4	**4d**: 4-$MeOC_6H_4$	55	1:99
5	**4e**: (*E*)-PhCH=CH	73	1:> 99
6	**4f**: *n*-Pr	69	1:> 99
7	**4g**: *i*-Pr	60	1:> 99
8	**4h**: Cy	58	1:> 99
9	**4i**: *t*-Bu	63	1:> 99
10	**4j**: CO_2Et	76	1:> 99

[a] Determined by ^1H NMR analysis of the isolated material.

Remarkably, in almost all cases propargylations proceeded with complete regiospecificity; trace amounts of the corresponding allenic by-products **5** were only observed in the case of aromatic hydrazones **4b**–**d** (entries 2–4).

In summary, we have developed the highly selective allenylation and propargylation of *N*-acylhydrazones employing *in situ* prepared propargyl- and allenyltrichlorosilanes. These transformations display wide substrate scope for the C=N electrophiles used and proceed with excellent regiospecificity. It is noted that both trichlorosilyl nucleophiles were selectively prepared from the same propargyl halide, and that these carbon-carbon bond-forming reactions proceeded in *N,N*-dimethylformamide (DMF) without any metal catalysis. Hünig's base was shown to be an effective additive in terms of chemical yields. Further mechanistic studies on the selective silylation of propargylic halides and the role of Hünig's base as well as the development of organocatalytic asymmetric allenylation and propargylation are currently under investigation in this laboratory.

Experimental Section

General Procedure for the Selective *in situ* Preparation of Trichlorosilanes 2 and 3

To a stirred suspension of dry copper(I) chloride (5 mol %), dry copper(II) fluoride (5 mol %) or dry bis(2,4-pentanedionato)-nickel(II) (5 mol %) in anhydrous diethyl ether (0.5 M with respect to substrate **1a** or **1b**) at 20 °C were added dropwise *N,N*-diisopropylethylamine (4.0 equivs.), 3-chloroprop-1-yne (**1a**; 2.0 equivs.) or 3-bromoprop-1-yne (**1b**; 2.0 equivs.) and trichlorosilane (4.4 equivs.), successively (the amounts of the reagents are relative to one equivalent of the corresponding *N*-acylhydrazones). The mixture was stirred at 20 °C for 3–12 h and the product ratios **2**:**3** were determined by ^1H NMR analysis of an aliquot diluted with $CDCl_3$. Under the indicated optimized conditions, compounds **1a** or **1b** were completely consumed ($>99\%$ conversion) and exclusive formation of propargyltrichlorosilane (**2**; by using CuCl or CuF_2) or allenyltrichlorosilane [**3**; by using $Ni(acac)_2$] was observed (NMR yield ~75%; $>99:1$ ratios for each isomer).

General Procedure for the Selective Synthesis of Allenic Hydrazides 5 or Homopropargylic Hydrazides 6

The supernatant solution of the above *in situ* prepared trichlorosilanes **2** or **3** (~1.5 equivs. based on NMR yield) in diethyl ether was added dropwise *via* a syringe to stirred solutions of the corresponding hydrazones **4a**–**j** (1.0 equiv.) and *N,N*-diisopropylethylamine (0–10.0 equivs.) in DMF (0.1 M with respect to hydrazones **4a**–**j**) at 0 °C or 10 °C. The mixtures were stirred at 0 °C or 10 °C for 24 h, and quenched by dropwise addition of a solution of triethylamine in methanol (5 equivs. with respect to the used nucleophiles **2** or **3**). After stirring at 0 °C or 10 °C for an additional 30 min, the mixtures were warmed to room temperature and extracted with dichloromethane (three times, after addition of H_2O). The combined organic layers were washed (brine), dried (Na_2SO_4), filtered and concentrated under vacuum. The residues were purified by preparative thin-layer chromatography (PTLC; eluent: *n*-hexane/ethyl acetate = 3:1 to 10:1) to afford the corresponding allenic hydrazides **5a–j** (by using nucleophile **2**) or the corresponding homopropargylic hydrazides **6a–j** (by using nucleophile **3**).

***N′*-(1-Phenylhexa-4,5-dien-3-yl)benzohydrazide (5a)** (Table 2, entry 1): ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.89$ (dt, $J = 7.2$ Hz, $J = 8.1$ Hz, 2H), 2.25 (br s, 1H), 2.70 (dt, $J = 4.5$ Hz, $J = 8.1$ Hz, 2H), 3.56 (m, 1H), 4.81 (dd, $J = 2.4$ Hz, $J = 7.2$ Hz, 2H), 5.18 (dt, $J = 6.0$ Hz, $J = 7.2$ Hz, 1H), 7.10–7.28 (m, 5H), 7.38–7.59 (m, 3H), 7.70–7.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.4$, 34.3, 58.0, 77.3, 94.4, 125.9, 127.5, 128.3, 128.5, 128.6, 132.6, 134.7, 141.9, 167.0, 207.5; IR (neat): $\nu = 3286$, 2932, 1954, 1711, 1638, 1450, 895, 700 cm^{-1}; HR-MS (ESI): calcd. for $C_{19}H_{20}N_2O$ $[M+H]^+$: 292.1576; found: $m/z = 292.1578$.

***N′*-(1-Phenylhex-5-yn-3-yl)benzohydrazide (6a)** (Table 4, entry 1): ^{1}H NMR ($CDCl_3$): $\delta = 1.79$–2.02 (m, 3H), 2.08 (t, $J = 2.7$ Hz, 1H), 2.26–2.49 (m, 2H), 2.65–2.89 (m, 2H), 3.29 (tt, $J = 5.4$ Hz, $J = 11.7$ Hz, 1H), 7.11–7.24 (m, 5H), 7.31–7.55 (m, 3H), 7.65–7.85 (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 29.0$, 29.9, 32.1, 58.5, 71.2, 80.8, 126.2, 127.8, 128.1, 128.6, 129.0, 132.9, 134.9, 141.2, 166.7; IR (neat): $\nu = 3290$, 2926, 2118, 1705, 1644, 1451, 880, 698 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{20}N_2O$ $[M+H]^+$: 292.1576; found: $m/z = 292.1575$.

Acknowledgements

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[23] As suggested by a referee, control experiments were carried out by using *N*-methylated substrate **4a** and nucleophile **3** with or without Hünig's base (1.5 equivs.), under otherwise identical conditions. In all cases, no reaction occurred (only recovery of *N*-methylated substrate **4a**) thereby underlining the importance of the N–H moiety for the reactivity of *N*-acylhydrazones towards chlorosilane nucleophiles. Similar observations have already been reported: see refs.[10,14c, e]

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[27] Hünig's base also improved the yield of the allenylation of **4h** (R = Cy) with **2**. The desired product was obtained in 81% yield (ratio **5h**:**6h** = >99:1) in the presence of 1.5 equivalents of Hünig's base (cf. Table 2, entry 8: 70% yield without Hünig's base). Therefore, the mechanism depicted in Scheme 4 for nucleophile **3** seems to be equally valid for nucleophile **2**.