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Lewis Acid Mediated Vinyl-Transfer Reaction of Alkynes to *N*-Alkylimines by Using the *N*-Alkyl Residue as a Sacrificial Hydrogen Donor

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Dedicated to Professor Norbert De Kimpe on the occasion of his 65th birthday

Abstract: A variety of *N*-alkyl-α,α-dichloroaldimines were vinylated by terminal acetylenes in the presence of Lewis acids such as $In(OTf)_3$ or $BF_3{\cdot}OEt_2$ and hexafluoroisopropanol (HFIP) as an additive. The reaction proceeds at ambient temperature and leads to geometrically pure allylic β,β-dichloroamines. This approach is complementary to previously reported transition-metal-catalyzed vinyl-transfer methods, which are not applicable to aliphatic imines and are restricted to imines that contain an electron-withdrawing nitrogen substituent. In the present approach, terminal alkynes were used as a source of the vinyl residue, and the *N*-alkyl moiety of the imine acts as a sacrificial hydrogen donor. The additional advantage of this methodology is the fact that no external toxic or hazardous reducing agents or molecular hydrogen has to be used. This new methodology nicely combines a $C(sp^2)$–C(sp) bond formation, hydride transfer, and an unusual cleavage of an unactivated C–N bond, thereby giving rise to functionalized primary allylic amines. A detailed experimental study supported by DFT calculations of the mechanism has been done.

Keywords: alkynes · amines · imines · Lewis acids · redox chemistry

Introduction

Allylic amines are highly appreciated precursors in modern synthetic organic chemistry owing to their extensive use in the synthesis of therapeutic agents and bioactive natural products.[1] Moreover, their preparation as well as utilization in enantiomerically enriched forms has gained considerable awareness in recent years.[1,2] Although the vinylation of aldehydes and ketones to produce the corresponding allylic alcohols has been thoroughly devised,[3] the corresponding imine vinylation acknowledges a supplementary demand in organic synthesis.[1,4] In addition to the well-documented entries based on transition-metal-catalyzed allylic substitution by N-nucleophiles,[2b,c,e,f,5] a surrogate avenue to allylic amines based on the influential development of Soai et al.[6g] relied on the catalytic enantioselective vinylation of imines.[1,2,4,7] The latter case generally involves the catalytic enantioselective addition of vinylzinc reagents;[4f–g,7] these can be introduced in two steps, which involves in situ alkyne hydroboration and transmetalation of boron against zinc, applying $ZnMe_2$ to the corresponding imines. To serve this purpose, a broad range of enantioselective catalysts including both early-transition-metal catalysts (Hf, Ti, Zr) and late-transition-metal catalysts (Cu, Rh) have been employed.[4f] Apart from the drawbacks with regard to the in situ generation of the corresponding vinylzinc reagents, it is worth mentioning that the enantioselective addition of vinylzinc to imines is restricted to the activated *N*-acyl- and *N*-(diphenylphosphinoyl)imines.[6] Further advances on the synthesis of allylic amines, namely, the catalytic enantioselective addition of organoboron,[4f] organolithium, organotin, and organotitanium reagents to imines, employ several metal catalysts including rhodium catalysts.[4g,h] The development of transition-metal-catalyzed reductive coupling between imines and alkynes could bypass the use of organometallic reagents. Because these protocols need a terminal reductant such as hydrosilanes, hydrostannanes, organozinc reagents, organoboron reagents, or chromium(II) chloride, the formation of equimolar amounts of hazardous byproducts is still a point of concern.[4,6,7]

In this respect, progress has been made by Krische et al. by using molecular hydrogen as the cleanest and most cost-effective reducing agent for the catalytic enantioselective reductive alkyne–imine coupling.[4,8] Because most of the previously reported methods rely on either organometallic reagents as the source of the vinylic moiety or on hazardous reducing agents, the development of an efficient and mild

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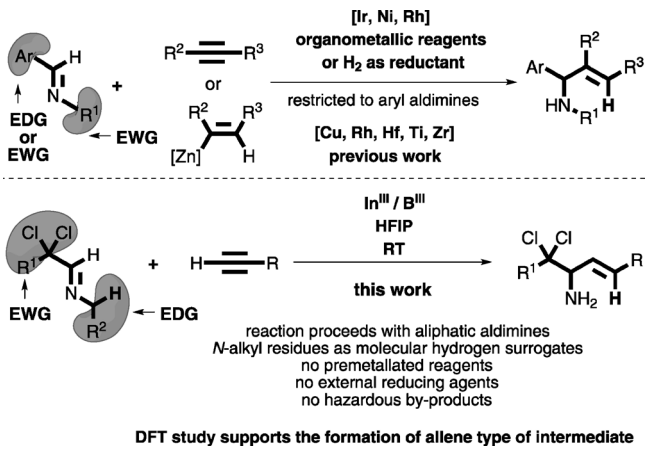


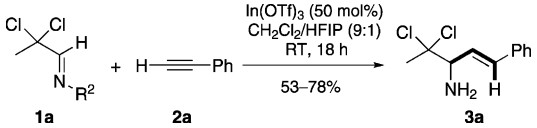
Scheme 1. Summary of reported work and this work.

protocol for the synthesis of allylic amines from alkynes and imines remains a challenging mission (Scheme 1). Basically, the envisioned conversion is characterized by an internal redox isomerization. Mechanistically, this process involves a [1,5]-hydride shift, catalyzed by Lewis or Brønsted acids, which have attracted much attention lately.[9] Herein, we would like to report on the synthesis of geometrically pure allylic β,β-dichloroamines by using a Lewis acid promoted reaction between α,α-dichloroaldimines and terminal alkynes. The reaction mechanism and feasibility of the vinylation process was supported by quantum mechanical calculations. In this method, reductive vinylation of the imine by alkynes is accomplished by hydrogen transfer from the *N*-alkyl residue. In addition to the novelty of the described reaction, this important class of electrophiles is not commonly studied, so conceivably there is a certain novelty to these reactions.[10a] In this context special reference should be made with regard to the chelation-controlled addition of in situ generated vinylzinc reagents to a *N*-tosyl-α-chloroaldimine.[6h] To the best of our knowledge, there is no report of a vinyl-transfer reaction that relies on a sacrificial *N*-alkyl residue that is responsible for the selective intramolecular reduction of alkyne to the corresponding *E* alkene. In addition, vinyl-transfer reactions that use aliphatic aldimines have not been studied (Scheme 1).

Results and Discussion

On the basis of our recent contribution[10b] on the synthesis of a new class of polychlorinated propargylic amines by using an indium(III)-catalyzed reaction between α,α-dichloroaldimines and terminal alkynes, our interest shifted to vinyl-transfer reactions, because the related polychlorinated allylic amines are also rarely studied structural moieties in modern organic synthesis. During the screening of the reaction conditions for the alkynylation of *N*-(2,2-dichloro-1-propylidene)amine (**1a**) with phenylacetylene (**2a**) in the presence of 25 mol% $FeCl_3$ as catalyst and dichloromethane as solvent, in addition to the formation of 4,4-dichloro-1-phenyl-*N*-propylpent-1-yn-3-amine (**4a**) in 16% yield, an unknown, albeit vinylated compound was also observed in 20% yield (yield calculated by ^{1}H NMR spectroscopy; Table 1, entry 1). After careful flash chromatography and structural elucidation, this compound was identified as (*E*)-4,4-dichloro-1-phenylpent-1-en-3-amine (**3a**).

Table 1. Preliminary screening of the reaction conditions for the synthesis of **3a**.[a]



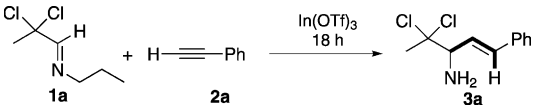
Entry	Lewis acid/[mol%]	*T* [°C]	Yield[b] [%]
1	$FeCl_3$/25	50	20[c]
2	$CuCl_2$/100	RT	37
3	$Cu(OTf)_2$/100	RT	36
4	AgOTf/100	RT	29
5	$In(OTf)_3$/100	RT	72
6	$Sc(OTf)_3$/100	RT	56
7	$InCl_3$/50	50	41
8	$ZnCl_2$/50	50	16

[a] Unless otherwise mentioned, 0.5 mmol of **1a** and 0.5 mmol of **2a** were reacted in a sealed vial. [b] Yields after acid–base workup. [c] Additionally 4,4-dichloro-1-phenyl-*N*-propylpent-1-yn-3-amine (**4a**) was observed in the ^{1}H NMR spectra.

Since it has been proven[11] that fluorinated alcohols can have magnificent effects on the efficiency, regioselectivity, and stereoselectivity of several chemical transformations, further screening of the reaction conditions in CH_2Cl_2 was performed using metal salts such as $CuCl_2$, $Cu(OTf)_2$, and AgOTf in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as an additive. We were gratified to observe that the yield of the desired product **3a** was increased to 37% (Table 1, entries 2–4) without the identifiable formation of any side products. Interestingly, the introduction of Lewis acids such as $In(OTf)_3$ and $Sc(OTf)_3$ in the presence of HFIP as an additive afforded (*E*)-4,4-dichloro-1-phenylpent-1-en-3-amine (**3a**) in good to high yields (Table 1, entries 5 and 6). Although $InCl_3$ and $ZnCl_2$ as Lewis acids were also able to accomplish the desired transformation, the yields of the allylic amine **3a** remained relatively low (Table 1, entries 7 and 8).

Next, this transformation was studied in further detail to find more optimal conditions (Table 2). Interestingly, it was observed that by decreasing the amount of $In(OTf)_3$ to 50 mol%, product **3a** was isolated in 65% yield when the reaction was conducted at ambient temperature, whereas product **3a** was formed in 53% yield by performing the reaction at 50°C (Table 2, entries 1 and 2). Notably, by substituting dichloromethane for toluene as a solvent, the yield of **3a** dropped dramatically (Table 2, entries 3 and 4). Further attempts using 25 and 10 mol% of $In(OTf)_3$ (Table 2, entries 5–7) and decreasing the reaction times (Table 2, entry 8) as well as the amounts of HFIP (Table 2, entry 9) only led to lower yields of **3a**. Moreover, it was found that

Table 2. Optimization of the reaction conditions for the synthesis of **3a**.[a]



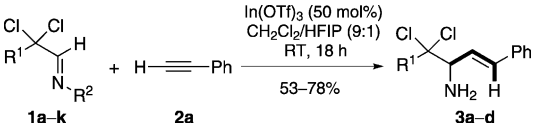
Entry	$In(OTf)_3$ [mol%]	Solvent (3.6 mL)	Additive	T [°C]	Yield[b] [%]
1	50	CH_2Cl_2	HFIP (0.4 mL)	50	53
2	50	CH_2Cl_2	HFIP (0.4 mL)	RT	65
3	50	$PhCH_3$	HFIP (0.4 mL)	RT	38
4	50	$PhCH_3$	HFIP (0.4 mL)	50	35
5	25	CH_2Cl_2	HFIP (0.4 mL)	RT	41
6	25	CH_2Cl_2	HFIP (0.4 mL)	50	33
7	10	CH_2Cl_2	HFIP (0.4 mL)	50	27
8	50	CH_2Cl_2	HFIP (0.4 mL)	RT	34[c]
9	50	CH_2Cl_2	HFIP (1 mmol)	RT	43
10	50	CH_2Cl_2	*t*BuOH (1 mmol)	RT	7[d]
11	50	CH_2Cl_2	TFA (1 mmol)	RT	0

[a] Unless otherwise mentioned, 0.5 mmol of **1a** and 0.5 mmol of **2a** were reacted in a sealed vial. [b] Yields after acid–base workup. [c] Reaction was carried out for 12 h. [d] Additionally, 4,4-dichloro-1-phenyl-*N*-propylpent-1-yn-3-amine (**4a**) was observed in the ^1H NMR spectra.

*t*BuOH as an additive was much less effective (Table 2, entry 10) as only 7% of the vinylated product **3a** was observed in the ^1H NMR spectra in addition to 69% of 4,4-dichloro-1-phenyl-*N*-propylpent-1-yn-3-amine (**4a**). On the other hand, the addition of 2 equivalents of trifluoroacetic acid (TFA) completely inhibited this transformation (Table 2, entry 11). Taking into account an acceptable yield of 65% of **3a** and considering the cost of $In(OTf)_3$, the optimal reaction conditions for this conversion were established when 0.5 mmol of **1a** and 0.5 mmol of **2a** were reacted in the presence of 50 mol% of $In(OTf)_3$ as catalyst in CH_2Cl_2/HFIP (9:1) for 18 h at ambient temperature (Table 2, entry 2).

With the optimal conditions at hand, the scope of this transformation was studied (Table 3). It was found that a broad range of α,α-dichloroaldimines **1** that contain both electron-donating (Table 3, entries 1–7) and electron-withdrawing substituents (Table 3, entries 8–10) were tolerated under the reaction conditions and produced the corresponding product **3** in yields that ranged from 53 to 78% (Table 3).

Table 3. $In(OTf)_3$-mediated synthesis of **3** using various α,α-dichloroaldimines **1**.[a]

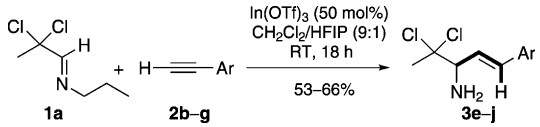


Entry	**1**	R^1	R^2	Product **3**	Yield **3** [%][b]
1	**a**	Me	*n*Pr	**a**	65
2	**b**	Me	Et	**a**	60
3	**c**	Me	*i*Pr	**a**	78
4	**d**	Me	allyl	**a**	54
5	**e**	Me	Bn	**a**	73
6	**f**	Et	Et	**b**	53
7	**g**	Et	*n*Pr	**b**	59
8	**h**	*i*Pr	allyl	**c**	63[c]
9	**i**	Cl_3C	*n*Pr	**d**	53
10	**j**	Cl_3C	*i*Pr	**d**	58
11	**k**	Cl_3C	allyl	**d**	65

[a] Unless otherwise mentioned, 0.5 mmol of **1a** and 0.5 mmol of **2a** were reacted in a sealed vial. [b] Yields after acid–base workup. [c] GC yield.

The scope of the arylacetylene was also evaluated. A broad range of electron-donating groups such as methyl, ethyl, *tert*-butyl, and methoxy groups, and an electron-withdrawing group such as a fluoro group (in the presence of methyl group) on the benzene ring survived under the reaction conditions and produced 4,4-dichloro-1-arylpent-1-en-3-amines **3** in yields that ranged from 53 to 66% (Table 4).

Table 4. $In(OTf)_3$-mediated reaction between **1a** and various arylacetylenes **2**.[a]



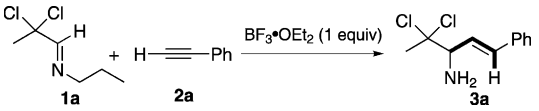
Entry	**2**	Ar	Product **3**	Yield **3** [%][b]
1	**b**	4-MeC_6H_4	**e**	65
2	**c**	4-EtC_6H_4	**f**	53
3	**d**	4-*t*BuC_6H_4	**g**	66
4	**e**	3-$MeOC_6H_4$	**h**	62
5	**f**	4-BrC_6H_4	**i**	55[c]
6	**g**	4-F-3-MeC_6H_3	**j**	61

[a] Unless otherwise mentioned, 0.5 mmol of **1a** and 0.5 mmol of **2a** were reacted in a sealed vial. [b] Yields after acid–base workup. [c] GC yield.

Further extensions of the substrate scope revealed that the introduction of extra steric hindrance on the α,α-dichloroaldimines leads to both vinylation product and alkynylation product in a 1.3/1 ratio (see the Supporting Information). It was also found that the presence of strong electron-withdrawing groups such as chloro and nitro groups in both the *ortho* and *para* position of the arylacetylene completely hindered the formation of the vinylated product and gave rise to the 4,4-dichloro-1-aryl-*N*-propylpent-1-yn-3-amines **4** (see the Supporting Information). Surprisingly, the reaction of **1a** with 4-bromophenylacetylene under the optimized conditions afforded the corresponding allylic β,β-dichloroamine **3g** (Table 4, entry 5). The simultaneous presence of a strong electron-withdrawing fluoro group and an electron-donating methyl group on the arylacetylene (Table 4, entry 6) or an electron-donating alkyl group on the arylacetylene (Table 4, entries 1–3) also promoted the selective formation of the corresponding vinylated compounds **3**.

In an attempt to avoid the formation of variable amounts of alkynylated side products, $In(OTf)_3$ was replaced by a stronger Lewis acid (Table 5). To our delight, the reaction of α,α-dichloroaldimine **1a** and phenylacetylene in the presence of 1 equivalent of $BF_3{\cdot}OEt_2$ in CH_2Cl_2/HFIP (9:1) for 5 h under reflux conditions gave rise to **3a** in 40% yield without any trace of the propargylic amine **4a** (Table 5, entry 1). After a careful screening of the reaction conditions by using $BF_3{\cdot}OEt_2$ as a Lewis acid (Table 5, entries 1–7), it

Table 5. Optimization of the reaction conditions for the BF_3·OEt_2-mediated reaction between **1a** and **2a**.[a]

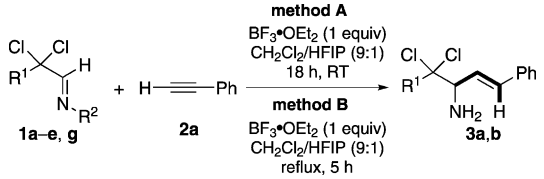


Entry	Reaction conditions	Solvent/Additive	Yield **3a** [%][b]
1	reflux, 5 h	CH_2Cl_2/HFIP (9:1)	40
2	reflux, 2 h	CH_2Cl_2/HFIP (9:1)	32
3	RT, 5 h	CH_2Cl_2/HFIP (9:1)	45
4	RT, 18 h	CH_2Cl_2/HFIP (9:1)	62
5	RT, 5 h	EtOH	0
6	reflux, 5 h	CH_2Cl_2/TFE[c] (9:1)	23
7	reflux, 5 h	CH_2Cl_2/PhOH (9:1)	30

[a] Unless otherwise mentioned, 0.5 mmol of **1a** and 0.5 mmol of **2a** were reacted in a sealed vial. [b] Yields after acid–base workup. [c] 2,2,2-Trifluoroethanol.

can be concluded that the reaction between **1a** and **2a** in the presence of 1 equiv of BF_3·OEt_2 as Lewis acid in CH_2Cl_2/HFIP (9:1) for 18 h at ambient temperature (method A) or under reflux conditions for 5 h (method B) afforded the maximum yield of the product **3a** (Table 5, entries 1 and 4). These reaction conditions were used to investigate the scope of the various imines **1** and arylacetylenes **2** (Tables 6 and 7).

Table 6. BF_3·OEt_2-mediated reaction between **1** and **2a**.[a]

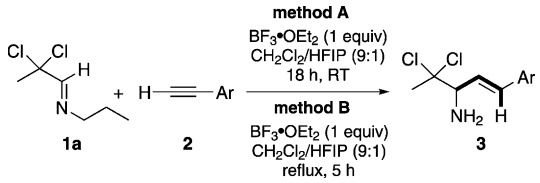


Entry	**1**	R^1	R^2	Product **3**	Method/Yield **3** [%][b]
1	**a**	Me	*n*Pr	**a**	A/62
					B/40
2	**b**	Me	Et	**a**	A/53
					B/44
3	**c**	Me	*i*Pr	**a**	A/55
					B/45
4	**d**	Me	allyl	**a**	A/51
					B/30
5	**e**	Me	Bn	**a**	A/57
					B/49
6	**g**	Et	*n*Pr	**b**	A/49

[a] Unless otherwise mentioned, 0.5 mmol of **1** and 0.5 mmol of **2a** were reacted in a sealed vial. [b] Yields after acid–base workup.

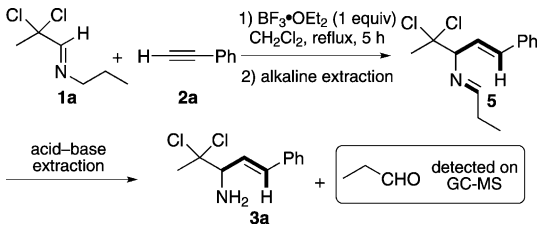
To elucidate the mechanistic aspects of this vinylation process, several experiments were performed. The reaction of *N*-*tert*-butyl-(2,2-dichloro-1-propylidene)amine and phenylacetylene (**2a**) under reaction conditions B did not lead to the expected vinylated product, which clearly indicates that the presence of at least one hydrogen atom on the α′-carbon atom of *N*-alkyl residue is mandatory. Moreover, the formation of propanal as a side product was identified by GC-MS by performing a reaction between 1 equivalent of *N*-(2,2-dichloro-1-propylidene)propylamine (**1a**) and phenylacetylene (**2a**) in the presence of 1 equivalent of BF_3·OEt_2 in CH_2Cl_2 under reflux conditions for 5 h (Scheme 2). After alkaline extraction of the reaction mixture using 0.5 M NaOH, ^{1}H NMR spectroscopic analysis of the crude mixture showed the presence of 12 mol% of unreacted starting imine **1a**, 24 mol% of phenylacetylene (**2a**), and 64 mol% of the 2-aza-1,4-diene *N*-(4,4-dichloropent-1-en-3-yl)propylidenamine (**5**). The latter product is readily hydrolyzed to (*E*)-4,4-dichloro-1-phenylpent-1-en-3-amine (**3a**) after acid–base extraction of the crude reaction mixture (Scheme 2). When the same reaction was carried out in CH_2Cl_2, but now in the presence of the cosolvent HFIP (9:1), alkaline extraction of the resulting crude mixture gave rise to a very complicated ^{1}H NMR spectrum. Again, acid–base extraction afforded the corresponding product **3a**.

Table 7. BF_3·OEt_2-mediated reaction between **1a** and **2**.[a]



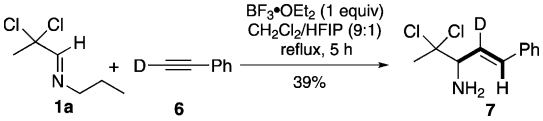
Entry	**2**	Ar	Product **3**	Method/Yield **3** [%][b]
1	**b**	4-MeC_6H_4	**e**	A/63
				B/57
2	**c**	4-EtC_6H_4	**f**	A/41
				B/23
3	**e**	3-$MeOC_6H_4$	**h**	A/55
				B/44
4	**g**	4-F-3-MeC_6H_3	**j**	A/53
				B/36

[a] Unless otherwise mentioned, 0.5 mmol of **1a** and 0.5 mmol of **2** were reacted in a sealed vial. [b] Yields after acid–base workup.



Scheme 2. Evidence for the formation of intermediate **5**.

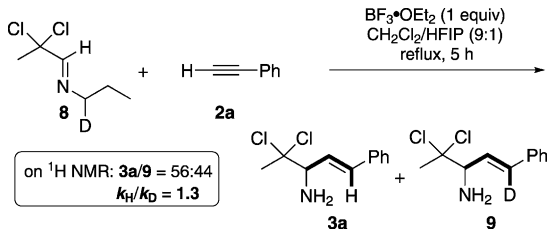
Next, the addition of 1 equivalent of [D]phenylacetylene (**6**) to *N*-(2,2-dichloro-1-propylidene)propylamine (**1a**) was investigated in the presence of 1 equivalent of BF_3·OEt_2 in CH_2Cl_2/HFIP (9:1) under reflux conditions for 5 h (Scheme 3). After acid–base extraction of the crude reaction



Scheme 3. BF_3·OEt_2-mediated synthesis of **7**.

mixture, the vinylated product **7** was obtained in 39% yield. Interestingly, the deuterium atom in product **7** was still residing on its original carbon atom. This result clearly excludes the possibility of the deprotonation of phenylacetylene prior to the addition to **1a**. On the other hand, when the same reaction was performed in the presence of 50 mol% of $In(OTf)_3$ in CH_2Cl_2/HFIP (9:1) at ambient temperature for 18 h, to some extent (17%) the formation of the nondeuterated **3a** was observed in the ^1H NMR spectrum. This can be explained by the formation of phenylacetylene (**2a**) from in situ generated indiumacetylides, which are reprotonated by HFIP during the course of the reaction.

An intramolecular kinetic isotope effect (KIE) study was conducted with substrate **8**. For this, monodeuterated *N*-(2,2-dichloro-1-propylidene)propylamine **8** was treated with phenylacetylene (**2a**) in the presence of 1 equivalent of BF_3•OEt_2 in CH_2Cl_2/HFIP (9:1) under reflux conditions for 5 h (Scheme 4). After acid–base extraction, a mixture that



Scheme 4. Determination of the intramolecular deuterium kinetic isotope effect.

consisted of vinylated products **3a** and **9** was obtained. The formation of the deuterated (*E*)-[D]4,4-dichloro-1-phenylpent-1-en-3-amine-1 (**9**) proves the migration of the deuterium atom from the α′-carbon atom of the *N*-alkyl residue to the C-2 of the phenylacetylene (**2a**).

Considering the formation of the nondeuterated and deuterated addition products **3a** and **9** in a 1.3/1.0 ratio ($k_H/k_D = 1.3$), one can assume that the breaking of the carbon–deuterium bond in the starting material **8** is subjected to a kinetic isotope effect, regardless of mechanism.[12] However, this does not automatically indicate that the breaking of the C–H(D) bond in **1a** (**8**) is involved in the rate-determining step.[12b]

The proposed stepwise mechanism for the vinylation process with phenylacetylene is supported by density functional theory calculations that involved *N*-(2,2-dichloroethylidene)ethanamine as the model imine. The calculations were performed at the B3LYP/TZ2P level of theory using Gaussian 09.[13] Corrections for the solvent, a mixture of dichloromethane and HFIP (9:1), were accounted for by using the standard self-consistent reaction field (SCRF) model. The equilibrium geometries for the reagents, the reaction product, the intermediate, and the transition states involved, and the reaction coordinates derived are shown schematically in Figure 1. The Cartesian coordinates for the different geometries, the maximum forces obtained during the geometry optimizations, and the lowest vibrational frequencies that prove the nature of the stationary points are summarized in the Supporting Information.

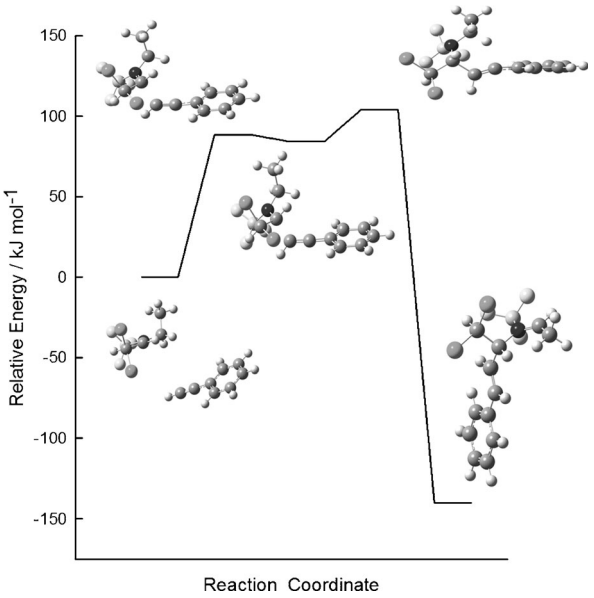
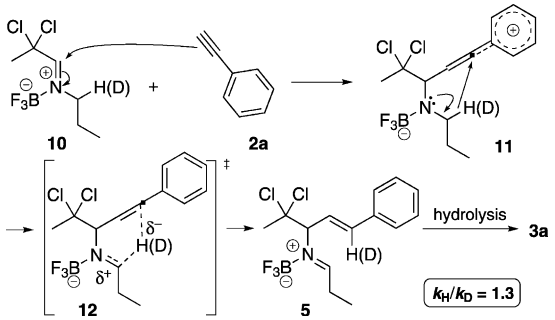


Figure 1. Reaction coordinate obtained for the vinylation process involving *N*-(2,2-dichloroethylidene)ethanamine and phenylacetylene. The calculations were performed at the B3LYP/TZ2P level, using a self-consistent reaction field (SCRF) model to correct for solvent stabilizations. The energies for the transition states, the intermediate, and the reaction products relative to that of the reagents are 88.3, 104.2, 84.6, and −140.3 kJ mol^{-1}, respectively.

The stepwise mechanism (Scheme 5) starts with the coordination of BF_3•OEt_2 or another Lewis acid with the nitrogen atom of the α,α-dichlorinated imine **1**, as described recently in literature,[14] thus making the imino-carbon atom more electrophilic. The presence of at least two chloro



Scheme 5. Proposed stepwise mechanism for the BF_3•OEt_2-mediated synthesis of **3a**.

atoms in the α position of the imine function is also essential to make the azomethine carbon atom in the BF_3 complex **10** even more electrophilic. In the stepwise mechanism (Scheme 5), nucleophilic addition of phenylacetylene (**2a**) to the activated imine **10** takes place, thereby resulting in the formation of an allene-type intermediate **11**, which

expels a hydride ion by means of a β-hydride elimination mechanism. Such a mechanism is also known for alkyllithium compounds that contain a β-hydrogen atom, and hence act as hydride donors.[15] Conceptually related [1,5]-hydride-transfer reactions, from carbon atoms α to the nitrogen atom to an electron acceptor, such as an activated vinyl group,[9d,f,k,l] iminium bond,[9e] imine,[9c,h,i] or aldehyde[9j] have been reported in the literature.

The calculated dipole moments of the transition states and intermediate **11** are large and will be strongly stabilized by the solvent (TS1 = 16.0 debye, IM = 18.8 debye, TS2 = 15.96 debye). This probably explains why this reaction only can proceed in the presence of HFIP. HFIP is a highly polar solvent and has a bigger dielectric constant ($E_T^N = 1.068$, $\varepsilon = 16.6$) than dichloromethane ($E_T^N = 0.309$, $\varepsilon = 8.9$).[16] The intermediate carbocation **11** finally undergoes a formal 1,5-hydride shift to form azadiene **5**, which after hydrolysis delivers the final product **3a** (Scheme 5). This conversion resembles the Crabbé homologation, which involves the one-pot preparation of allenes by Cu^I-catalyzed coupling of alkynes with formaldehyde by using a sacrificial secondary amine as a hydride donor.[17] In this process an in situ formed propargylic amine undergoes a 1,5-sigmatropic rearrangement of hydrogen, thereby giving rise to the allene and an imine. Although similar, this mechanism is not applicable in our case, since no intermediate propargylic amine is formed. In a control reaction of 4,4-dichloro-1-phenyl-*N*-propylpent-1-yn-3-amine (**4a**)[10b] with 1 equivalent of BF_3·OEt_2 in CH_2Cl_2/HFIP (9:1) under reflux conditions for 5 h, no reaction was observed.

To further rationalize the results derived for phenylacetylene, DFT calculations were also initiated for the reaction of *N*-(2,2-dichloro-1-propylidene)propylamine (**1a**) with an aliphatic alkyne, such as propyne (**2h**). The equilibrium geometries for the reagents, the reaction product, and the transition state involved, and the reaction coordinate that suggests a concerted one-step mechanism are shown schematically in Figure 2. As before, the details for the geometries obtained are given in the Supporting Information. The activation energy for the concerted process equals 129.0 kJ mol^{-1}, which is much higher than the values of 88 (TS1) and 104 kJ mol^{-1} (TS2) found for the same reaction of **1a** with phenylacetylene. Of course, in the case of the reaction of **1a** with propyne, no stabilized allene type of intermediate is formed, which explains the one-step character of this conversion (Scheme 6).

On the basis of this prediction, we decided to investigate the reaction of *N*-(2,2-dichloro-1-propylidene)propylamine (**1a**) with 1-hexyne and cyclohexylacetylene in the presence of BF_3·OEt_2 in CH_2Cl_2/HFIP (9:1). No reaction was observed at all when these reactions were performed at room temperature. However, by heating the reaction mixture in sealed vials at 50 °C, the allylic β,β-dichloroamines **3l** and **3m** were obtained in 61 and 75 % yield, respectively (Scheme 7).

The higher temperature required for the conversion of aliphatic alkynes is in accordance with the higher activation

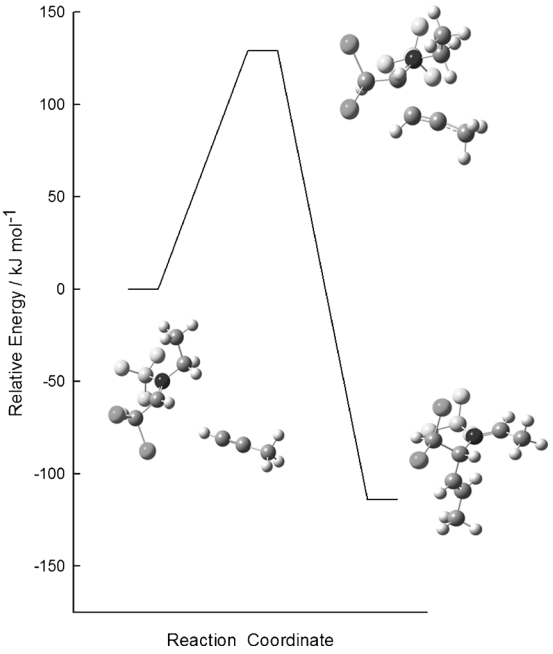
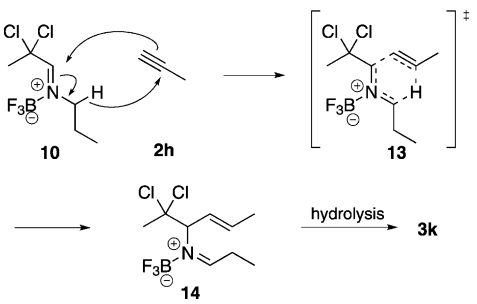
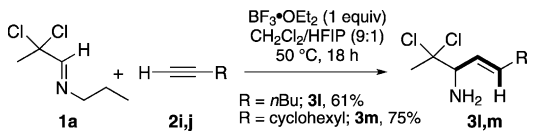


Figure 2. Reaction coordinate obtained for the vinylation process involving *N*-(2,2-dichloroethylidene)ethanamine and propyne. The calculations were performed at the B3LYP/TZ2P level, using an SCRF model to correct for solvent stabilizations. The activation energy for the concerted reaction equals 129.0 kJ mol^{-1}.



Scheme 6. Proposed concerted mechanism for the BF_3·OEt_2-mediated synthesis of **3k**.



Scheme 7. BF_3·OEt_2-mediated reaction between **1a** and alkylacetylenes **2i**,**j**.

energy calculated for the concerted process. It is worth mentioning that when the same reactions were carried out in the presence of $In(OTf)_3$ at room temperature or even at 50 °C, no vinylated products were formed. Instead, the corresponding propargylic β,β-dichloroamines **4l** and **4m** were isolated in 82 and 86 % yield, respectively (see the Supporting Information).

Conclusion

In conclusion, various *N*-alkyl-α,α-dichloroaldimines were successfully vinylated by using a wide variety of terminal alkynes as the vinyl source in the presence of Lewis acids such as $In(OTf)_3$ and $BF_3{\cdot}OEt_2$. The allylic β,β-dichloroamines, all with *E* configurations, formed in this conversion could be easily isolated in pure form by simple acid–base extraction. This transformation can only proceed in the presence of HFIP, and uses the *N*-alkyl residue of the imine as a reducing equivalent, which ultimately leads to its removal from the nitrogen atom of the allylic amine. The mechanism of this unprecedented vinyl-transfer reaction was investigated by a detailed experimental study and is supported by DFT calculations. For arylacetylenes a stepwise reaction path is followed, whereas aliphatic terminal acetylenes react in a concerted fashion. In both mechanisms a 1,5-hydride shift from the *N*-alkyl moiety of the imine to the alkyne holds a central place.

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[1] For reviews, see: a) M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689–1708; b) R. B. Cheikh, R. Chaabouni, A. Laurent, P. Mison, A. Nafti, *Synthesis* **1983**, 685–700.

[2] For reviews, see: a) E. M. Skoda, G. C. Davis, P. Wipf, *Org. Process Res. Dev.* **2012**, *16*, 26–34; b) R. Takeuchi, S. Kezuka, *Synthesis* **2006**, 3349–3366; c) H. Miyabe, Y. Takemoto, *Synlett* **2005**, 1641–1655; d) L. E. Overman, N. E. Carpenter, *Org. React.* **2005**, *66*, 1–107; e) B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813–5837; f) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943; for selected examples, see: g) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2004**, *116*, 4031–4034; *Angew. Chem. Int. Ed.* **2004**, *43*, 3941–3944; h) P. Wipf, C. Kendall, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2003**, *125*, 761–768; i) R. B. Grossman, W. M. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **1991**, *113*, 2321–2322; j) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165.

[3] For reviews, see: a) M. Hatano, K. Ishihara, *Chem. Rec.* **2008**, *8*, 143–155; b) J. Montgomery, G. J. Sormunen, *Top. Curr. Chem.* **2007**, *279*, 1–24; c) D. J. Ramón, M. Yus, *Chem. Rev.* **2006**, *106*, 2126–2208; d) C. García, V. S. Martin, *Curr. Org. Chem.* **2006**, *10*, 1849–1889; e) D. J. Ramón, M. Yus, *Angew. Chem.* **2004**, *116*, 286–289; *Angew. Chem. Int. Ed.* **2004**, *43*, 284–287; f) P. Wipf, R. L. Nunes, *Tetrahedron* **2004**, *60*, 1269–1279; g) P. Wipf, C. Kendall, *Chem. Eur. J.* **2002**, *8*, 1778–1784; h) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; for selected examples, see: i) M.-Y. Ngai, A. Barchuk, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 280–281; j) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361; k) S.-J. Jeon, H. Li, C. Garcia, L. K. La Rochelle, P. J. Walsh, *J. Org. Chem.* **2005**, *70*, 448–455; l) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539.

[4] a) C.-Y. Zhou, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 10955–10957; b) A. Barchuk, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 8432–8433; c) E. Skucas, J. R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 7242–7243; d) M.-Y. Ngai, A. Barchuk, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 12644–12645; e) J. R. Kong, C.-W. Cho, M. J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276; f) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2003**, *115*, 1402–1405; *Angew. Chem. Int. Ed.* **2003**, *42*, 1364–1367; for recent reviews, see: g) J. F. Bower, M. J. Krische, *Top. Organomet. Chem.* **2011**, *34*, 107–138; h) R. L. Patman, J. F.; Bower, I. S. Kim, M. J. Krische, *Aldrichimica Acta* **2008**, *41*, 95–104.

[5] a) G. Helmchen, in *Iridium Complexes in Organic Synthesis* (Eds.: L. A. Oro, C. Claver), Wiley-VCH, Weinheim, **2009**, p. 211; b) L. Acemoglu, J. M. J. Williams, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1 and 2 (Eds.: E. Negishi, A. de Meijere, Wiley, New York, **2002**, p. 1689; for reviews, see: c) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264–303; *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; d) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675–691.

[6] a) I. Sato, K. Hosoi, R. Kodaka, K. Soai, *Eur. J. Org. Chem.* **2002**, 3115–3118; b) X. Zhang, W. Lin, L. Gong, A. Mi, X. Cui, Y. Jiang, M. C. K. Choi, A. S. C. Chan, *Tetrahedron Lett.* **2002**, *43*, 1535–1537; c) C. Jimeno, S. Reddy, L. Sola, A. Moyano, M. A. Pericas, A. Riera, *Org. Lett.* **2000**, *2*, 3157–3159; d) P. Brandt, C. Hedberg, K. Lawonn, P. Pinho, P. G. Andersson, *Chem. Eur. J.* **1999**, *5*, 1692–1699; e) D. Guijarro, P. Pinho, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 2530–2535; f) P. G. Andersson, D. Guijarro, D. Tanner, *J. Org. Chem.* **1997**, *62*, 7364–7375; g) K. Soai, T. Hatanaka, T. Miyazawa, *J. Chem. Soc. Chem. Commun.* **1992**, 1097–1098; h) G. R. Stanton, P.-O. Norrby, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2012**, *134*, 17599–17604.

[7] For reviews, see: a) K.-I. Yamada, K. Tomioka, *Chem. Rev.* **2008**, *108*, 2874–2886; b) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454–470; c) T. Vilaivan, W. Bhanthumnavin, Y. Sritana-Anant, *Curr. Org. Chem.* **2005**, *9*, 1315–1392; d) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; e) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407–1438.

[8] a) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734–2793; b) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912–2942; c) *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; d) *Heterogeneous Catalysis and Fine Chemicals IV* (Eds.: H. U. Blaser, A. Baiker, R. Prins), Elsevier, Amsterdam, **1997**.

[9] For a review see: a) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142; for selected examples see: b) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180–12181; c) C. Zhang, C. Kanta De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416–417; d) S. Murarka, C. Zhang, M. D. Konieczynska, D. Seidel, *Org. Lett.* **2009**, *11*, 129–132; e) C. Zhang, S. Murarka, D. Seidel, *J. Org. Chem.* **2009**, *74*, 419–422; f) M. C. Haibach, I. Deb, C. Kanta De, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 2100–2103; g) K. Mori, S. Sueoka, T. Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 2424–2426; h) P. A. Vadola, I. Carrera, D. Sames, *J. Org. Chem.* **2012**, *77*, 6689–6702; i) Y.-P. He, H. Wu, D.-F. Chen, J. Yu, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 5232–5237; j) I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos, N. Maulide, *Angew. Chem.* **2012**, *124*, 1986–1989; *Angew. Chem. Int. Ed.* **2012**, *51*, 1950–1953; k) D.-F. Chen, Z.-Y. Han, Y.-P. He, J. Yu, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 12473–12476; *Angew. Chem. Int. Ed.* **2012**, *51*, 12307–12310; l) L. Zhang, L. Chen, J. Lv, J.-P. Cheng, S. Luo, *Chem. Asian J.* **2012**, *7*, 2569–2576.

[10] a) B. I. Roman, N. De Kimpe, C. V. Stevens, *Chem. Rev.* **2010**, *110*, 5914–5988; b) C. C. Malakar, B. U. W. Maes, K. Abbaspour Tehrani, *Adv. Synth. Catal.* **2012**, *354*, 3461–3467.

[11] a) S. Stas, K. Abbaspour Tehrani, *Tetrahedron* **2007**, *63*, 8921–8931; b) K. K. Nanda, B. W. Trotter, *Tetrahedron Lett.* **2005**, *46*, 2025–2028; c) C. Catmela, J. I. García, J. A. Mayoral, L. Salvatella, *Can. J. Chem.* **1994**, *72*, 308–311; d) H. C. Brown, E. J. Mead, C. J. Shoaf, *J. Am. Chem. Soc.* **1956**, *78*, 3613–3614; e) D. Vuluga, J. Legros, B. Crousse, A. M. Z. Slawin, C. Laurence, P. Nicolet, D. Bonnet-Delpon, *J. Org. Chem.* **2011**, *76*, 1126–1133.

[12] a) M. H. El-Badri, D. Willenbring, D. J. Tantillo, J. Gervay-Hague, *J. Org. Chem.* **2007**, *72*, 4663–4672; b) E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120–3126; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.

[13] Gaussian 09, Revision A.2, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[14] a) Y. Ma, E. Lobkovsky, D. B. Collum, *J. Org. Chem.* **2005**, *70*, 2335–2337; b) K. B. Aubrecht, M. D. Winemiller, D. B. Collum, *J. Am. Chem. Soc.* **2000**, *122*, 11084–11089; c) J. E. Davies, P. R. Raithby, R. Snaith, A. E. H. Wheatley, *Chem. Commun.* **1997**, 1797–1798.

[15] a) B.-A. Feit, S. Shapira, A. Herbst, *Tetrahedron* **1995**, *51*, 317–328; b) R. Withnall, I. R. Dunkin, R. Snaith, *J. Chem. Soc. Perkin Trans. 2* **1994**, 1973–1977; c) M. Majewski, *Tetrahedron Lett.* **1988**, *29*, 4057–4060.

[16] C. Reichardt, in *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., Wiley-VCH, Weinheim, **1990**.

[17] a) S. Searles, Y. L. Nassim, M.-T. R. Lopes, P. T. Tran, P. Crabbé, *J. Chem. Soc. Perkin Trans. 1* **1984**, 747–751; b) J. Kuang, S. Ma, *J. Org. Chem.* **2009**, *74*, 1763–1765; c) H. Nakamura, T. Kamakura, M. Ishiku, J.-F. Biellmann, *J. Am. Chem. Soc.* **2004**, *126*, 5958–5959.

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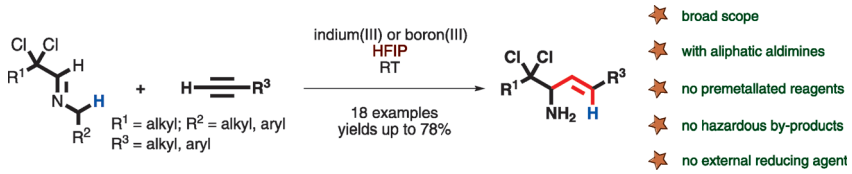

Vinylation records: A variety of *N*-alkyl-α,α-dichloroaldimines can be vinylated by terminal acetylenes in the presence of Lewis acids such as $In(OTf)_3$ or $BF_3{\cdot}OEt_2$ and hexafluoroisopropanol (HFIP) as an additive. The reaction leads to geometrically pure allylic β,β-dichloroamines (see scheme). Terminal alkynes were used as a source of vinyl residue, and the *N*-alkyl moiety of the imine acts as a sacrificial hydrogen donor.

Vinylation

*C. C. Malakar, S. Stas, W. Herrebout, K. Abbaspour Tehrani** ..... ▮▮▮▮–▮▮▮▮

Lewis Acid Mediated Vinyl-Transfer Reaction of Alkynes to *N*-Alkylimines by Using the *N*-Alkyl Residue as a Sacrificial Hydrogen Donor