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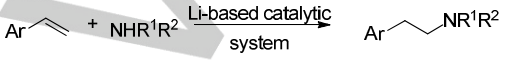
Lithium-catalysed anti-Markovnikov intermolecular hydroamination reactions of vinylarenes and simple secondary amines

Stéphane Germain,[a] Meije Lecoq,[a] Emmanuelle Schulz,[a,b]* and Jérôme Hannedouche[a,b]*

Abstract: Various β-arylethylamine derivatives have been straightforwardly obtained by lithium-catalysed anti-Markovnikov selective intermolecular hydroamination reactions of secondary aliphatic amines and vinylarenes. Use of as little as 1.5 mol % $LiCH_2TMS$ as solid base in THF proved to be an efficient room-temperature protocol for delivering the targeted products in up to complete conversion. Both reaction partners were moreover used in equivalent amounts, thus best respecting the concepts of sustainable chemistry for the easy preparation of lead structures for pharmaceutically active compounds.

The direct addition reaction of an amine across a carbon-carbon double bond, the so-called hydroamination reaction, is one of the most step- and atom- economical methodology for the preparation of nitrogen-containing compounds from relatively inexpensive and ubiquitous amines and olefins.[1] During the past two decades, intense research activities have been dedicated to the development of efficient catalytic systems for the (stereo)selective intra- and intermolecular hydroamination of olefins displaying Markovnikov regioselectivity.[1] In contrast, the anti-Markovnikov regioselectivity remains poorly developed and this despite the industrial importance of linear amine products. Indeed, only sporadic catalytic systems based on organic compounds,[2] late transition metals,[3] rare-earth elements,[4] alkaline earth [5] or alkali [6,7] metals have exhibited such regioselectivity mainly on vinylarenes to provide β-arylethylamines as key synthons. To our knowledge, the anti-Markovnikov selective hydroamination of amines and simple aliphatic alkenes has not yet been reported, highlighting the significant challenge with such development.[8] Although the field of alkali metal-promoted hydroamination reaction emerged in the early 1950s, most of the reported studies have been limited in terms of scope to a few amine/olefin partners and have been conducted under harsh reactions conditions. It is only recently that the groups of Beller,[6c] and later Hultzsch,[6a] have truly explored the scope of alkali-metal catalyzed anti-Markovnikov hydroamination of vinylarenes with *N*-benzylpiperazine and primary/secondary amines respectively, under gentler conditions (Scheme 1). Beside the fact that these studies have provided useful protocols for the preparation of a range of linear amine products, there is still room for improvement in terms of catalyst efficiency and scope. It is in this context that we disclose herein our studies towards the development of a convenient room-temperature protocol for the direct anti-Markovnikov addition of simple secondary aliphatic amines on vinylarenes using solely solid trimethysilylmethyl lithium as a very efficient ligand-free lithium-based (pre)catalyst in low loading (1.5 mol%) (Scheme 1)



Beller et al. (2004):	*Hultzsch et al. (2007):*	***This work:***
n-BuLi (20 mol%)	$LiN(TMS)_2$ (5 mol%)	$LiCH_2TMS$ (1.5 mol%)
THF, rt, 24h	TMEDA (5 mol%)	$[D_8]$THF, 21°C,
78-100% conv.	C_6D_6, 120°C, 1-137h	0.5-120h,
12 examples	36-96% yield	38->99% conv.
R^1,R^2 = -$[(CH_2)_2N(Bn)(CH_2)_2]$-	10 examples	15 examples

Scheme 1. State of the art in lithium-catalysed anti-Markovnikov intermolecular hydroamination of vinylarenes and secondary amines.

A few years ago, our group has reported the first application of chiral diaminobinaphthyl dilithium salts as easily available and efficient alkali-metal based (pre)catalysts for the asymmetric cyclohydroamination of amino-1,3-dienes with the highest stereo- and enantioselectivites described to date (up to 93:7 dr and 71 % ee).[9,10] The methodology was further extended to the enantioselective intramolecular hydroamination of primary and secondary amines tethered to alkenes at room temperature with ee's up to 58%.[9b,11] These efficient lithium-based catalysts were in-situ prepared by a straightforward protocol resulting from the combination of *N*-substituted (*R*)-(+)-1,1'-binaphthyl-2,2'-diamines such as (*R*)-H_2**L**$^{1\text{-}3}$ (Figure 1) and $LiCH_2TMS$ in a 1:2.5 ratio. Analysis on the structure of the (pre)catalyst and control experiments have clearly demonstrated that a small excess of base (relative to the stoichiometry required to deprotonate the diamines) was essential to the system reactivity.[9a] We describe here our results concerning the ability of this specific catalytic system to promote the more challenging intermolecular anti-Markovnikov hydroamination reactions of vinylarenes and our observations that lead to the development of a competent ligand-free trimethysilylmethyl lithium-based (pre)catalyst for this transformation.

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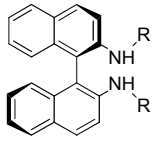
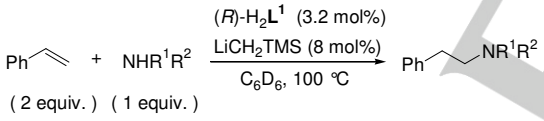


(*R*)-H_2**L**^{1}, R = CH_2Ph
(*R*)-H_2**L**^{2}, R = cyclopentyl
(*R*)-H_2**L**^{3}, R = *i*-Pr

Figure 1. *N*-substituted (*R*)-(+)-1,1'-binaphthyl-2,2'-diamines H_2**L**$^{1\text{-}3}$

First efforts were thus drawn towards intermolecular hydroamination reactions of styrene as a benchmark substrate. The reaction of *N*-methylbenzylamine **1** (1 equiv.) and styrene (2 equiv) in the presence of our previously reported catalytic system (*R*)-H_2**L**^{1}:$LiCH_2TMS$ in a 1:2.5 ratio delivered solely the anti-Markovnikov product **4** with 92 % conversion in one hour (Table 1, entry 1) at 100°C in benzene. Pyrrolidine **2** reacted delightfully similarly under the same conditions, albeit conversion could not exceed 81 %, even after prolonged reaction time. Intermolecular hydroamination could also be performed in the presence of a primary amine, since use of benzylamine **3** delivered with the same regioselectivity the mono-hydroamination product **6** in nearly complete conversion, even if the reaction time dramatically increased for this reaction (Table 1, entry 3). As far as we know, this specific selectivity has until now not been observed in other reports for alkali salts catalysed hydroamination reaction. Indeed, under a similar excess of styrene, the reported $LiN(TMS)_2$/TMEDA system (10 mol%) leads to the formation of bis(hydroamination) product as side-product.[6a]

Table 1. Intermolecular hydroamination of styrene and primary and secondary amines in [D_6]benzene.[a]



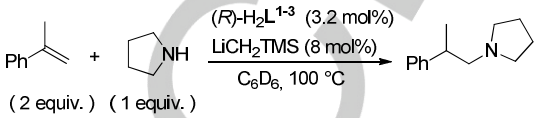
1 R^1 = Bn, R^2 = Me
2 R^1, R^2 = -$(CH_2)_4$-
3 R^1 = Bn, R^2 = H
4 R^1 = Bn, R^2 = Me
5 R^1, R^2 = -$(CH_2)_4$-
6 R^1 = Bn, R^2 = H

Entry	Amine	Product	Time [h]	NMR yield [%]
1	**1**	**4**	1	92
2	**2**	**5**	0.75	81[b]
3	**3**	**6**	48	98[c]

[a] reaction was performed at 100°C in [D_6]benzene allowing for NMR conversion determination with ferrocene as internal standard. [b] maximal conversion. [c] only mono-hydroamination anti-Markovnikov product is observed.

According to the observed reactivity, disubstituted olefins were then studied, and α- and β-methyl-styrene and *trans*-stilbene were allowed to react with either *N*-methylbenzylamine **1** or pyrrolidine **2**, under the same reactions conditions as described above. Unfortunately, almost all reactions performed were unsuccessful, and the engaged substrates were recovered as unchanged mixtures even after prolonged reaction time. Only the use of pyrrolidine **2** in the presence of two equivalents of α-methyl-styrene delivered the linear product **7** with a conversion of 42 % after 5h of reaction (Table 2, entry 1). Extending the reaction time to 24h did not improve the yield (Table 2, entry 2).

Table 2. Enantioselective intermolecular hydroamination of α-methylstyrene and pyrrolidine **2** in [D_6]benzene.[a]



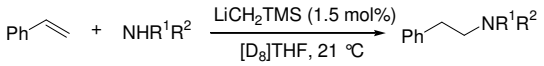
2 R^1, R^2 = -$(CH_2)_4$- **7** R^1, R^2 = -$(CH_2)_4$-

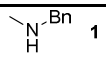
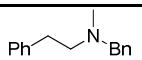
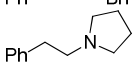
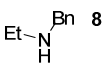
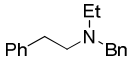
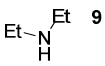
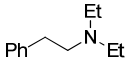
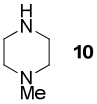
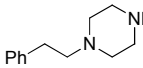
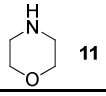
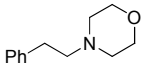
Entry	Ligand	Time [h]	NMR yield [%][b]
1	(*R*)-H_2**L**^{1}	5	42
2		24	43[c]
3	(*R*)-H_2**L**^{2}	24	13[c]
4	(*R*)-H_2**L**^{3}	24	8[c]
5	(±)-H_2**L**^{1}	24	67[c]
6	-	24	78[c]
7	-	6	92[d]

[a] reaction was performed at 100°C in [D_6]benzene allowing for NMR conversion determination with ferrocene as internal standard. [b] racemic product is observed. [c] prolonged reaction time to 120h does not improve the yield. [d] at rt in [D_8]THF.

Unfortunately, **7** was recovered as a racemic mixture. The same trend was observed in the presence of other chiral ligands (*R*)-H_2**L**$^{2\text{-}3}$ (Table 2, entries 3-4). Fortunately, use of ligand (±)-H_2**L**^{1} as a racemic mixture allowed for an improved conversion (67 % after 24h, Table 2, entry 5), that could be increased up to 78 % using 8 mol% of $LiCH_2TMS$ without any additional ligand (Table 2, entry 6). We thus assume that the dramatic negative influence of the presence of the ligands on the reaction rate is due to the formation of inactive lithium amide aggregates, as already observed by Beller *et al.*.[6b] Delightfully, replacement of [D_6]benzene by [D_8]THF permitted the reaction to be performed at room temperature with 8 mol % of $LiCH_2TMS$ providing **7** with a high conversion of 92 % in only 6h (Table 2, entry 7). This more polar and coordinating solvent is indeed known to possibly reduce the lithium derivatives aggregation state in solution.[12]

Table 3. Intermolecular hydroamination of styrene and secondary amines in $[D_8]THF$.[a]

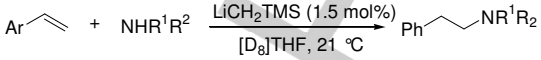


Entry	Amine	Product	Time [h]	NMR yield [%][b]
1	 **1**	 **4**	1	>99 (82)
2	 **2**	 **5**	1	>99 (71)
3	 **8**	 **12**	5	38
4	 **9**	 **13**	2	>99 (84)
5	 **10**	 **14**	0.5	>99
6	 **11**	 **15**	0.75	>99 (90)

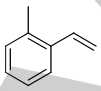
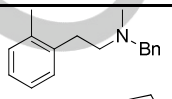
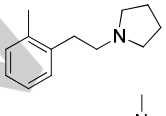
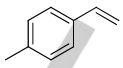
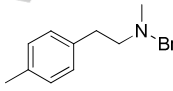
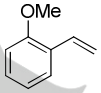
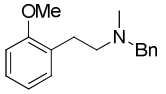
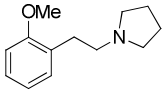
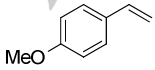
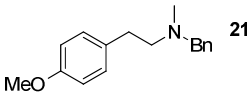
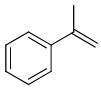
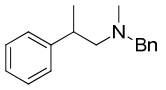
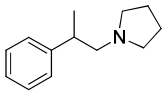
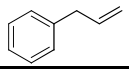
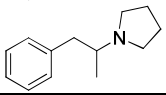
[a] reaction conditions : amine/styrene = 1/1, $LiCH_2TMS$ (1.5 mol %), Cp_2Fe (0.4 eq.), $[D_8]THF$, 21°C. [b] NMR conversion determined against ferrocene as internal standard and isolated yield in brackets.

These softener reaction conditions were next applied to the anti-Markovnikov selective hydroamination of styrene and various secondary amine partners under lower catalyst loading of base and an equimolar mixture of both reaction partners. Use of only 1.5 mol% of $LiCH_2TMS$ at room temperature in $[D_8]THF$ delivered regioselectively only anti-Markovnikov products. The results obtained are gathered in Table 3. Hence, application of these conditions to the reaction between *N*-methylbenzylamine **1** and styrene gave quantitatively benzyl-methyl-phenethyl-amine **4** in one hour (Table 3, entry 1) and the same result was obtained with pyrrolidine **2** (Table 3, entry 2). Both products **4** and **5** were nicely isolated in high yields. Under similar conditions of temperature, the reported $LiN(TMS)_2$/TMEDA system (10 mol%) affords **5** in 82% isolated yield after 107h,[6a] highlighting the remarkable activity of our system comparatively to the literature. Due to steric hindrance, transformation in the presence of *N*-ethylbenzylamine **8** took place more slowly and the targeted hydroamination product **12** was only formed in 38 % yield after 5 h reaction (Table 3, entry 3) whereas diethylamine **9** reacted with a high rate producing diethyl-phenethyl-amine **13** with a complete conversion in only 2 h. *N*-methylpiperazine **10** and morpholine **11** underwent analogously a fast hydroamination reaction with styrene giving rise to the targeted products **14** and **15** in both high yield and short reaction time (Table 3, entries 5-6). As a comparison, the addition of *N*-benzylpiperazine (1 equiv.) and styrene (2 equiv.) catalysed by *n*-BuLi (20 mol%) in THF at room temperature provides the linear product in 80% yield after 24h of reaction.[6c,13]

Table 4. Intermolecular hydroamination of vinylarenes and *N*-methylbenzylamine **1** or pyrrolidine **2** in $[D_8]THF$.[a]



1 R^1 = Bn, R^2 = Me
2 R^1, R^2 = -$(CH_2)_4$-

Entry	Amine	Product	Time [h]	NMR yield [%][b]
1		 **16**	1	>99
2		 **17**	1	>99
3		 **18**	1	97
4		 **19**	0.25	>99
5		 **20**	0.25	>99
6		 **21**	8	37
7		 **22**	96	59
8		 **7**	96	58
9[c]		 **23**	120	98 (65)

[a] reaction conditions : amine/styrene = 1/1, $LiCH_2TMS$ (1.5 mol %), Cp_2Fe (0.4 eq.), $[D_8]THF$, 21°C. [b] NMR conversion determined against ferrocene as internal standard and isolated yield in brackets. [c] $LiCH_2TMS$ (8 mol %).

Having these conditions in hands, the scope of the reaction was extended to the use of *N*-methylbenzylamine **1** and pyrrolidine **2** in intermolecular hydroamination reactions with various arenes. Different substituents on styrene-based derivatives were firstly investigated, and transformations were then attempted in the presence of less activated alkene derivatives (Table 4). Styrene derivatives diversely substituted on the phenyl ring were firstly investigated and methylstyrene compounds (with the methyl substituent located either in the *ortho* or *para*-position) allowed the production of all targeted compounds **16-18** with a complete conversion within one hour

(Table 4, entries 1-3). Introduction of a methoxy substituent in the *ortho* position proved also very efficient in terms of reaction rate, whereas an important deceleration occurred with the introduction of this donating group in *para* position (Table 4, entries 4,5 *vs*.6). The reactivity difference between the *ortho*- and *para*-position of the methoxy-substituent may be rationalised by the favourable participation of the *ortho*-methoxy, in contrast to the *para*-methoxy, to the coordination of the carbon-carbon double bond to the reactive lithium intermediate. This trend was previously noticed with yttrium-based catalytic system.[4a] Unfortunately, 9-vinylanthracene did not react under these reaction conditions and no transformation occurred when it was introduced in stoichiometric quantity in the presence of either *N*-methylbenzylamine **1** or pyrrolidine **2**. α-Methyl-styrene was then investigated as starting material and compounds **22** and **7** were delightfully obtained, albeit complete conversion could not be reached even after prolonged reaction time of up to 4 days (Table 4, entries 7 and 8). However, α,β-disubstituted olefins remained unreactive and no transformation could be observed involving 1,2-dihydro-naphthalene, propenylbenzene, *cis*- and *trans*-stilbene and neither secondary amines. Fortunately, pyrrolidine **2** reacted in the presence of allylbenzene (8 mol % $LiCH_2TMS$), and compound **23** was isolated in 65% yield after a complete conversion.[6d] Simple less reactive olefins such as pent-1-ene or oct-1-ene failed to undergo the hydroamination reaction with pyrrolidine **2** and only double bond isomerisation could be observed. Attempts to use more reactive substrates, such as norbornene or cyclohexadiene have not been successful either and 2-vinyl- or 4-vinylpyridine underwent only fast polymerization under these conditions.

To conclude, we have described a mild procedure allowing for lithium-catalysed intermolecular hydroamination of vinylarenes and simple secondary aliphatic amines. Comparatively to preceding reports, use of $LiCH_2TMS$ as base permitted for the reaction to be run at room temperature and with low catalyst amount (1.5 mol %). Under these conditions, various β-arylethylamines were rapidly obtained in high yields from diverse styrene derivatives and secondary amines. Further efforts are still needed to allow for a control of the stereoselectivity of the newly formed stereogenic centres what remains highly challenging in *anti*-Markovnikov intermolecular hydroamination promoted by chiral lithium salts.[14]

Experimental Section

General. All manipulations were performed under an Ar atmosphere by using standard Schlenk or glovebox techniques. [D_6]Benzene and [D8]THF were dried with sodium benzophenone ketyl, transferred under vacuum, and stored over activated 3 Å molecular sieves. Ligand H_2**L**$^{1\text{-}3}$ were prepared according to a reported procedure.[15] All amines and vinylarenes were dried with calcium hydride and transferred under vacuum. 9-vinylanthracene was dried under vacuum. All amines and vinylarenes were further dried for at least 2 h with 3Å molecular sieves with a few drops of solvent prior to use. (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine was purchased from Sigma-Aldrich and used without any further purification. Ferrocene was purchased from Sigma-Aldrich and was purified by sublimation prior to use. Solid $LiCH_2TMS$ was obtained by cold-recrystallisation of a 1M pentane solution of $LiCH_2TMS$ purchased from Sigma-Aldrich. Bruker AM250, AV300, AV360 NMR spectrometers operating at 250, 300, 360 MHz, respectively, were used to record the ^{1}H NMR spectra. Chemical shifts were referenced internally according to the Me_4Si resonance. Mass spectra were recorded by using a Bruker MicrOTOF-Q spectrometer.

General procedure for anti-Markovnikov hydroamination of vinylarenes in the presence of chiral ligand: A solution of $LiCH_2TMS$ (3.5 mg, 37.5 µmol) in [D_6]benzene or [D_8]THF (200 µL) was added to a solution of the appropriate ligand (15 µmol) in [D_6]benzene or [D_8]THF (250 µL). The reaction mixture was allowed to stir for 5 min at r.t. before being transferred to a vial containing the appropriate amine (0.45 mmol), the styrene derivative (0.90 mmol) and ferrocene (33.5 mg, 0.18 mmol). The reaction mixture was then introduced into a screw-tap or a J. Young-tap NMR tube and the progress of the reaction was monitored by ^{1}H NMR spectroscopy using ferrocene as internal standard.

General procedure for anti-Markovnikov hydroamination of vinylarenes and primary and secondary amines catalysed by ligand free- $LiCH_2TMS$: A solution of $LiCH_2TMS$ (0.6 mg, 6 µmol) in [D_8]THF (400 µL) was transferred to a vial containing the appropriate amine (0.4 mmol), the appropriate vinylarene (0.4 mmol) and ferrocene (0.08 mmol). The reaction mixture was then introduced into a screw-tap or a J. Young-tap NMR tube and the progress of the reaction was monitored by ^{1}H NMR spectroscopy using ferrocene as internal standard. The reaction mixture was quenched with ethanol and the product was purified on a preparative TLC plate.

***N*-Benzyl-*N*-methyl-2-phenylethanamine (4)**: Rf=0.48 (pentane/EtOAc 75:25); colorless oil (83 mg, 0.37 mmol, 82%); ^{1}H NMR (300 MHz, $CDCl_3$, 294 K): δ=2.34 (s, 3 H), 2.64–2.77 (m, 2 H), 2.83–2.95 (m, 2 H), 3.62 (s, 2 H), 7.20–7.39 ppm (m, 10 H); ^{13}C{^{1}H} NMR (75 MHz, CDCl3, 294 K): δ=34.1, 42.3, 59.4, 62.3, 126.1, 127.1, 128.4, 128.5, 128.9, 129.2, 139.1, 140.7 ppm; MS (EI): m/z (%):134.0 (78), 90.9 (100); HRMS (ESI): m/z: calcd for $C_{16}H_{20}N$ (226.1590): $[M+H]^+$; found 226.1587. These data are in agreement with previously published data.[6a]

1-Phenethylpyrrolidine (5): Rf=0.09 (pentane/EtOAc 75:25); yellow oil (50 mg, 0.29 mmol, 71%); ^{1}H NMR (300 MHz, $CDCl_3$, 294 K): δ=1.75–1.94 (m, 4 H), 2.55–2.68 (m, 4 H), 2.68–2.78 (m, 2 H), 2.83–2.91 (m, 2 H), 7.16–7.37 ppm (m, 5 H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$, 294 K): δ=23.7, 35.9, 54.4, 58.5, 126.3,128.6, 128.8, 140.5 ppm; MS (EI): m/z (%): 83.9 (100); HRMS (ESI): m/z: calcd for $C_{12}H_{18}N$ (176.1434): $[M+H]^+$; found 176.1433. These data are in agreement with previously published data.[6a]

***N,N*-diethyl-2-phenylethanamine (13):** Rf = 0.51 (DCM/MeOH 90:10); colorless oil (60 mg, 0.34 mmol, 84%); ^{1}H NMR (360 MHz, $CDCl_3$, 294 K) δ=1.04 (t, 6 H), 2.41 (q, 4 H), 2.64-2.74 (m, 2 H), 2.81-2.90 (m, 2 H), 7.16-7.37 ppm (m, 5H). ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$, 294 K) δ=12.5, 36.7, 51.6, 58.2, 126.6, 128.7, 128.9, 140.8 ppm; HRMS (ESI): m/z: calcd for $C_{12}H_{20}N$ (178.1590): $[M+H]^+$; found 178.1591. These data are in agreement with previously published data.[16]

***N*-(2-phenethyl)morpholine (15):** Rf = 0.48 (DCM/MeOH 90:10); colorless oil (69 mg, 0.36 mmol, 90 %); ^{1}H NMR (300 MHz, $CDCl_3$, 294 K) δ=2.36-2.72 (m, 6 H), 2.79-2.87 (m, 2 H), 3.92-4.02 (m, 4 H), 7.12-7.33 ppm (m, 5 H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 294 K) δ=46.3, 52.6, 58.4, 66.9, 126.2, 128.7, 128.9, 140.0 ppm; HRMS (ESI): m/z: calcd for $C_{12}H_{18}NO$ (192.1382): $[M+H]^+$; found 192.1385. These data are in agreement with previously published data.[17]

***N*-(2-phenypropyl)pyrrolidine (23):** Rf = 0.10 (EtOAc/pentane 75:25); colorless oil (55 mg, 0.29 mmol, 65 %); ^{1}H NMR (250 MHz, [D_8]THF, 294

K) δ=0.90(d, *J*=6.0 Hz, 3 H), 1.61-1.73 (m, 4 H), 2.39 (dd, *J*=9.3, 12.8 Hz 1 H), 2.46-2.70 (m, 5 H), 2.99 (dd, *J*=3.8, 12.8 Hz, 7.01-7.38 (m, 5 H); $^{13}C\{^{1}H\}$ NMR (62.5 MHz, [D_8]THF, 294 K) δ=16.4, 23.6, 41.1, 50.1, 59.6, 125.1, 127.4, 128.8, 139.9; HRMS (ESI): m/z: calcd for $C_{13}H_{20}N$ (190.1590): $[M+H]^+$; found 190.1596. These data are in agreement with previously published data.[18]

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Keywords: Intermolecular hydroamination • Lithium • Anti-Markovnikov addition • Secondary amines • Vinylarenes

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[13] Use of primary amines in these conditions led to a significantly lower reactivity than observed with secondary amines. Indeed, benzylamine and cyclopentylamine allowed the formation of anti-Markovnikov products in only 25 and 32 % yield respectively, after 5 h reaction, but with a perfect selectivity in monohydroamination products. Prolongated reaction time (144h) for benzylamine led to 85% NMR yield of anti-Markovnikov product from monohydroamination.

[14] To our knowledge, the highest ee value reported to date for the enantioselective anti-Markovnikov addition of amines and styrene derivatives promoted by chiral lithium-based catalyst is 14%, see reference 6a, as unique report.

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Layout 2:

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Various β-arylethylamine derivatives have been straightforwardly obtained by lithium-catalysed anti-Markovnikov selective intermolecular hydroamination reactions of vinylarenes and secondary aliphatic amines. Use of as little as 1.5 mol % $LiCH_2TMS$ as solid base in THF proved to be an efficient room-temperature protocol for delivering the targeted products in up to complete conversion and under stoichiometric partner conditions.

Stéphane Germain, Meije Lecoq, Emmanuelle Schulz, and Jérôme Hannedouche**

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Lithium-catalysed anti-Markovnikov intermolecular hydroamination reactions of vinylarenes and simple secondary amines