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From terminal alkynes directly to branched amines

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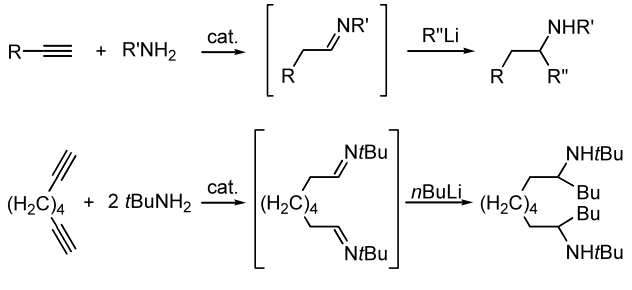
Abstract—The one-pot synthesis of several branched secondary aliphatic amines is described. Hydroamination of terminal alkynes with aliphatic primary amines in the presence of $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ gives the corresponding aldimines as intermediates. Reaction of these in situ produced aldimines with organolithium reagents (*n*-BuLi, PhLi) provides the α-branched amines in an easy way in upto 78% overall yield. © 2003 Elsevier Science Ltd. All rights reserved.

The preparation of existing and new α-branched secondary amines is of significant interest to organic synthesis due to their use in chemistry, agriculture and medicine.[1] Clearly, there exists a number of different approaches to synthesize this class of compounds.[2] However, most methods involve multiple steps and often overall yields are only mediocre. Upto now the preferred method involves 1,2-addition of organometallic reagents to available aldimines, obtained by the condensation of an aldehyde with a primary amine.[2a–f] The main disadvantage of this condensation is the production during the reaction of water, which has to be removed. Hence, laborious product purification and isolation have to be done. In addition, side-reactions such as aldol-condensations take place, giving lower yields of the desired products. Importantly, imines derived from bulky amines such as *tert*-butylamine are difficult to prepare.[2a] Thus, only a few derivatives of this type exist so far.

Obviously, it would be attractive to synthesize such amines directly in a one-pot approach from easily available starting materials. In this regard the recent work of Saidi and co-workers is interesting to note. Here, a one-pot Mannich-type reaction of nucleophiles with in situ preformed imines mediated by lithium perchlorate gave the corresponding products.[2h]

Recently, the hydroamination of alkynes has been developed to a convenient tool for the synthesis of alkynes.[3] This route is the most atom-efficient way to obtain imines or amines, because no side-product (e.g. water) is produced during the reaction. Both the use of early[4] and late[5] transition metal catalyst systems have been described for this transformation.

Unfortunately, alkyne hydroaminations of terminal alkynes give the corresponding ketimines and not aldimines, due to the Markovnikov addition of the amine to the alkyne. Last year we reported the first *anti*-Markovnikov hydroamination of terminal alkynes[6] in the presence of $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ (Rosenthal's catalyst).[7] Based on this reaction we present a simple way to obtain branched secondary aliphatic amines starting from the corresponding terminal alkynes, primary aliphatic amines and organolithium reagents in a one-pot reaction (Scheme 1).



cat. = $Cp_2Ti(\eta^2\text{-}Me_3Si{-}{\equiv}{-}SiMe_3)$

R = *n*-C_4H_9, *n*-C_6H_{13}, $PhCH_2$, (*cyclo*-C_5H_9)CH_2, Me_2N-CH_2
R' = *t*-C_4H_9, *s*-C_4H_9, (*t*-C_4H_9)MeCH
R" = *n*-C_4H_9, Ph, Me

Scheme 1.

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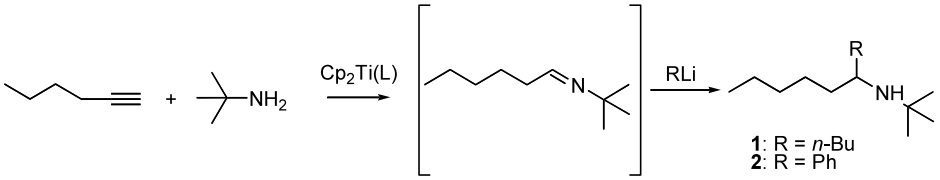
The $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$-catalyzed *anti*-Markovnikov hydroamination of terminal alkynes proceeds highly selectively with bulky aliphatic amines.[6] Hence, we chose the reaction of 1-hexyne and *tert*-butylamine to investigate the optimal conditions for the alkylation of the corresponding aldimine with *n*-BuLi and PhLi. Some representative examples are shown in Table 1. It is important to note that an excess (1.5–2.5 equiv.) of organolithium reagent is necessary for full conversion of the starting materials. As expected, the reaction of *n*-BuLi proceeds faster and requires a smaller excess of the organometallic reagent compared to PhLi (Table 1, entries 1–3 versus 4–7). Surprisingly, the yields were low using MeLi (Table 2, entry 3), even with longer reaction times and a higher excess of the organolithium reagent compared to the reaction with *n*-BuLi and PhLi.

To gain more insight into the scope and limitations of our method, we have tested the reaction of various terminal alkynes (1-octyne, 3-phenyl-1-propyne, 3-cyclopentyl-1-propyne, phenylacetylene, *N*,*N*-dimethylpropargylamine, 1,7-octadiyne) with different bulky aliphatic amines (*tert*-butylamine, *sec*-butylamine and 3,3-dimethyl-2-butylamine) using the previously found optimal conditions (Tables 2 and 3). The addition of *n*-BuLi was faster with the linear aliphatic substituted imines compared to aromatic and cyclic aliphatic substituted ones (Table 2, entries 1 and 7 versus 5 and 9). This observation can be explained by steric effects. In case of PhLi the differences were not so pronounced. All aliphatic alkynes gave the α-branched amines in good overall yield. In case of phenylacetylene, enolization of the aldimine to the corresponding enamine takes place under basic conditions. Therefore no addition of *n*-BuLi takes place. Of special interest is the synthesis of the diamines **11** and **12** (Table 2, entries 11 and 12) because the corresponding aldehydes which are required for alternative syntheses are not commercially available. In the latter case, double amination and double addition of *n*-BuLi proceeds with 50% overall yield, which corresponds to a yield of 85% for each reaction step, demonstrating the efficiency of the reaction. Reactions using *sec*-butylamine and 3,3-dimethyl-2-butylamine are shown in Table 3. The overall yields of α-branched amines **13** and **14** (55 and 65%, respectively) are somewhat lower than with the *tert*-butylamine analogue **8**. The reason for this difference is that the *anti*-Markovnikov:Markovnikov ratio of the corresponding intermediate imines is 3:1 and 4:1, compared to >99:1.[6] Fortunately, the alkylated products of the corresponding ketimines were obtained in both cases with very low yield (<3%) because the 1,2-addition to the aldimines is in general much faster than that of the ketimines. Hence, purification of **13** and **14** was not problematic at all. For compound **13** a mixture of two diastereomers was obtained (2.5:1). On the other hand, using (*R*)-3,3-dimethyl-2-butylamine only one diastereomer of compound **14** was observed. We explain this result by the better induction of stereoselectivity due to the increased steric bulk of the starting chiral amine.[8]

In conclusion we have shown for the first time that it is possible to combine titanium-catalyzed aminations of alkynes with the addition of organometallic reagents to a convenient one-pot procedure. Several branched secondary aliphatic amines can be synthesized by the hydroamination/alkylation sequence in reasonable to good yield. By using (*R*)-3,3-dimethyl-2-butylamine as chiral primary amine a diastereoselective synthesis of secondary amines is possible.

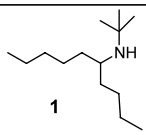
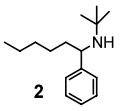
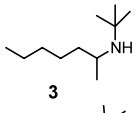
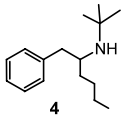
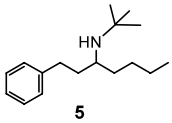
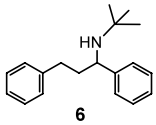
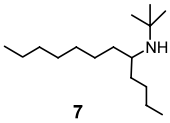
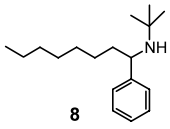
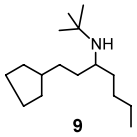
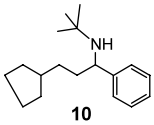
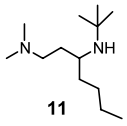
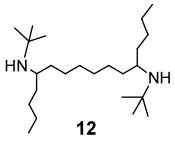
Table 1. One-pot reaction with 1-hexyne and *tert*-butylamine



Entry	NuLi	Product	Time (h) amination[a]/alkylation[b]	Ratio NuLi:alkyne	Yield (%)
1	*n*-BuLi	**1**	2/3	1.5	57
2	*n*-BuLi	**1**	2/3	**2**	**63**
3	*n*-BuLi	**1**	2/15	**2**	65
4	PhLi	**2**	2/3	**2**	25
5	PhLi	**2**	2/24	1.5	45
6	PhLi	**2**	2/24	2	53
7	PhLi	**2**	2/24	**2.5**	**61**

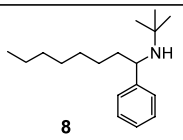
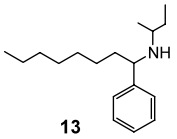
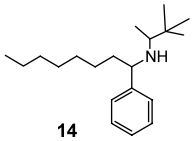
Conditions: a) Amination: 2.5 mol% of $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$, 85°C, 5 ml toluene, *tert*-butylamine:1-hexyne = 1.2:1. b) Alkylation: 30 min at −70°C, then rt (time given above). All yields were determined by GC using hexadecane or dodecane as internal standard and refer to 1-hexyne. The conversion of the aldimine was always 100%.

Table 2. One-pot reaction with *tert*-butylamine and different alkynes and NuLi[9]

Entry	Alkyne	NuLi	Product	Time (h) amination[a] / alkylation[b]	Ratio NuLi:alkyne	Yield [%]
1	1-Hexyne	*n*-BuLi	 **1**	2/3	2	63
2	1-Hexyne	PhLi	 **2**	2/24	2.5	61
3	1-Hexyne	MeLi	 **3**	2/48	4.5	< 20
4	Phenyl-acetylene	*n*-BuLi	 **4**	24/48	2	-
5	3-Phenyl-1-propyne	*n*-BuLi	 **5**	24/15	2	66
6	3-Phenyl-1-propyne	PhLi	 **6**	24/24	2.5	76
7	1-Octyne	*n*-BuLi	 **7**	2/3	2	72
8	1-Octyne[9]	PhLi	 **8**	2/24	2.5	78
9	3-Cyclopentyl-1-propyne	*n*-BuLi	 **9**	24/15	2	60
10	3-Cyclopentyl-1-propyne	PhLi	 **10**	24/24	2.5	70
11	*N,N*-Dimethylpropar-gylamine	*n*-BuLi	 **11**	2/3	2.0	49
12	1,7-Octadiyne[c]	*n*-BuLi	 **12**	2/3	4.0	50

Conditions: a) Amination: 2.5 mol% of $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$, 85 °C, 5 ml toluene, ratio *tert*-butylamine:alkyne = 1.2:1. b) Alkylation: 30 min. at -70 °C, then rt (time given above). All yields were determined by GC using hexadecane or dodecane as internal standard and refer to the alkynes. The conversion of aldimine is always 100%. c) Ratio *tert*-butylamine:alkyne = 4:1. The reaction was also carried out with 5-hexynenitrile and methylpropargylether, but no reaction was observed.

Table 3. One-pot reaction with different amines, 1-octyne and PhLi

Entry	Amine	Product	Time (h) amination[a] / alkylation[b]	Ratio PhLi:alkyne	Yield [%]
1	*tert*-butylamine	 **8**	2/24	2.5	78
2	*sec*-butylamine	 **13**	2/24	2.5	55[c]
3	*R*-3,3-dimethyl-2-butylamine	 **14**	2/24	2.5	65[d]

Conditions: a) Amination: 2.5 mol% of $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$, 85 °C, 5 ml toluene, 1.2:1 amine:1-octyne. b) Alkylation: 30 min. at −70 °C, then rt (time given above). All yields were determined by GC using hexadecane or dodecane as internal standard and refer to 1-octyne. The conversion of aldimine is always 100%. c) de = 71%. d) de = >95%.

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9. Typical reaction procedure (Table 2, entry 8): A solution of 2.2 ml (1.6 g, 14.9 mmol) 1-octyne and 1.9 ml (1.3 g, 17.8 mmol) *tert*-butylamine was treated with a solution of $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ (130 mg, 0.37 mmol, 2.5 mol%) in 5 ml toluene and heated to 85°C in a pressure tube. After 2 h the reaction mixture was cooled to −70°C and 20 ml PhLi (1.8 M, 37 mmol) were added. The mixture was stirred for 30 min at −70°C, warmed to room temperature and stirred for a further 24 h. Then the mixture was quenched with MeOH (3 ml), diluted with CH_2Cl_2 (10 ml), and treated with brine. The organic layer was separated, washed with water (3×20 ml) and dried over anhydrous $MgSO_4$. The filtrate was distillated in

vacuum. Product **8** was obtained at 105°C (0.1 mbar) as a light yellow oil (2.3 g, 60%, 78% (GC)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, 3H, CH_3), 0.91 (s, 9H, C-CH_3), 1.14–1.20 (m, 10H, CH_2), 1.5 (m, 2H, CH_2), 3.61 (t, $J=6.9$ Hz, 1H, CH), 7.2 (m, 5H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 23.1, 27.2, 29.6, 30.0 (CH_2), 30.6 (C-*C*H_3), 32.3, 41.2 (CH_2), 51.7 (C_q), 58.0 (CH), 126.6, 127.4, 128.5 (CH_{ar}), 148.6 (C_q). MS (EI, 70 eV): $m/z=262$ (M^++1), 246 (M^+–CH_3), 162 (M^+–C_7H_{15}), 91 ($C_7H_7^+$). All compounds are new and were characterized by NMR, MS, and IR.