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Ti(NMe$_2$)$_4$-catalyzed Markovnikov hydroamination of alkynes in the presence of *N*-heterocyclic carbenes and LiN(SiMe$_3$)$_2$

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Abstract—Intermolecular hydroamination of alkynes catalyzed by Ti(NMe$_2$)$_4$ was much improved with *N*-heterocyclic carbenes and LiN(SiMe$_3$)$_2$, by which high Markovnikov selectivity was attained for the coupling of nearly all alkynes and amines.

Hydroamination of alkynes and alkenes has been recognized as an important process for the synthesis of many higher nitrogen compounds in an atom-economical manner, and thus, various catalytic systems have been extensively explored, which include lanthanides and actinides, early and late transition metals as well as base catalysts.[1] For the intermolecular reaction of alkynes, group IV catalysts, particularly titanium complexes, have been successfully used since the pioneering work of Bergman and co-workers.[2] However, general Ti catalysts applicable to a wide range of alkynes and amines are still limited.[3] With respect to the regiochemistry of the reaction, *anti*-Markovnikov products are preferentially obtained with titanocene catalysts, and in contrast, Markovnikov isomers with nontitanocenes in general. The selectivity is, however, dramatically altered by the change of the alkynes, amines, and metal ligands. Accordingly, there are a few regiospecific systems for all substrates.[4]

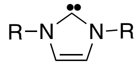
N-Heterocyclic carbenes (NHCs) have attracted much attention recently, because they can stabilize and activate the catalysts through specific coordination to the metal center, giving rise to revolutionary results in homogeneous catalysis chemistry.[5] A couple of titanium–NHC complexes have been reported,[6] but their reactivity for hydroamination is not investigated, surprisingly. Considering the reaction mechanism with Ti-catalysts,[7] the NHC ligands would facilitate the generation of a Ti-imido complex, an active species of the reaction, from the bisamide precursor and prevent its dimerization. Regiochemistry may also be changed by the steric and electronic effect of the ligand.[8] With these expectations, we studied the effect of NHCs on the intermolecular hydroamination of alkynes catalyzed by titanium complexes.

When the reaction of 1-octyne (**6a**) with aniline (**7a**) was carried out using Ti(NMe$_2$)$_4$ (**1**) and NHC **4a**, which is generated in situ from 1,3-dimethylimidazolium iodide and LiN(SiMe$_3$)$_2$ (**5a**), total yields of the products, **8a** and **9a**, were variable depending on the equivalent of **5a**: excess addition (2–3 equiv) usually gave better yields. Thus, the isolated NHCs **4**[9] were used to evaluate their effect accurately (Table 1).

$Ti(NMe_2)_4$ **1**

$CpTi(NMe_2)_3$ **2**

$Ti(CH_2Ph)_4$ **3**



4a: R = Me
4b: R = 2,4,6-Me$_3$Ph

M-N(SiMe$_3$)$_2$
5a: M = Li
5b: M = Na
5c: M = K

While the reaction with catalyst **1** alone gave the products in 42% yield, addition of the NHCs, **4a** and **4b**, rather decreased the reaction efficiency (runs 1–3). Interestingly, the yield was much improved to 82% in the presence of equimolar amounts of **1**, **4a**, and lithium silylamide **5a** (run 5). Control reaction using **1** and **5a**

Keywords: Hydroamination; Alkynes; Titanium catalysts; *N*-Heterocyclic carbenes; Lithium silylamides.

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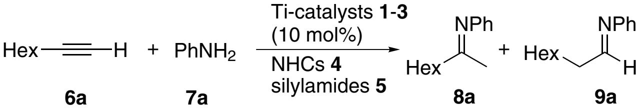
Table 1. Effect of the Ti-catalysts **1**–**3**, NHCs **4**, and silylamides **5**[a]



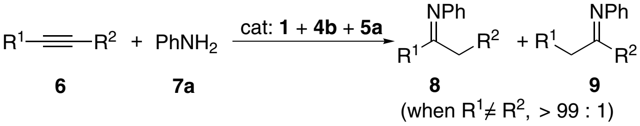
Run	Ti-catalyst 1–3	NHC 4	Silyamide 5	Ratio of 1–3/4/5	Total yield of **8a** and **9a**[b] (%)
1	**1**	None	None	1/0/0	42
2	**1**	**4a**	None	1/1/0	33
3	**1**	**4b**	None	1/1/0	28
4	**1**	None	**5a**	1/0/1	31
5	**1**	**4a**	**5a**	1/1/1	82
6	**1**	**4b**	**5a**	1/1/1	72
7	**1**	**4b**	**5a**	1/2/1	92
8	**1**	**4b**	**5a**	1/1/2	45
9	**1**	**4b**	**5a**	1/2/2	73
10	**1**	**4a**	**5b**	1/1/1	57
11	**1**	**4b**	**5b**	1/1/1	48
12	**1**	**4a**	**5c**	1/1/1	25
13	**1**	**4b**	**5c**	1/1/1	46
14	**2**	None	None	1/0/0	53
15	**2**	**4b**	**5a**	1/2/1	89
16	**3**	None	None	1/0/0	25
17	**3**	**4b**	**5a**	1/2/1	85

[a] Conditions: toluene, 100 °C, 2 h; **7a**/**6a** = 3.

[b] GC yield; the ratio of **8a**/**9a** was not determined.

gave inferior results (run 4). Of course, no hydroamination took place with **4a** and **5a** in the absence of **1**. The ratio of the three components, **1**, **4**, and **5**, was found to be important for the reaction efficiency, that is, the best yield was obtained when **1**/**4b**/**5a** was 1/2/1 (runs 6–9). Clear solvent effect was also observed under the conditions of run 7: toluene (92% yield) > cyclohexane (52%) > THF (37%) > DMF (28%). Of the silylamide additives **5**, Li salt **5a** exhibited superior effect to Na and K derivatives, **5b** and **5c** (runs 5, 6 vs 10–13). Moreover, it was proved that the three-component system was effective not only for the reaction with **1** but also for those with other Ti-catalysts, **2** and **3** (runs 14–17).

Table 2. The reaction of various alkynes with aniline[a]



Run	Alkyne **6**	R^1	R^2	Product **8**	Yield[b] (%)
1	**6a**	^{n}Hex	H	**8a**	92
2	**6b**	^{n}Bu	H	**8b**	98
3	**6c**	^{n}Oct	H	**8c**	98
4	**6d**	*c*-C_6H_{11}	H	**8d**	54
5	**6e**	^{t}Bu	H	**8e**	37
6	**6f**	$PhCH_2$	H	**8f**	46
7	**6g**	*c*-$C_6H_{11}CH_2$	H	**8g**	68
8	**6h**	$TMSOCH_2$	H	**8h**	12
9	**6i**	Et_2NCH_2	H	**8i**	15
10	**6j**	^{n}Pr	^{n}Pr	**8j**	57
11	**6k**	Ph	H	**8k**	52
12	**6l**	4-MePh	H	**8l**	85
13	**6m**	4-ClPh	H	**8m**	32
14	**6n**	Ph	Ph	**8n**	85
15	**6o**	Ph	Me	**8o**	89

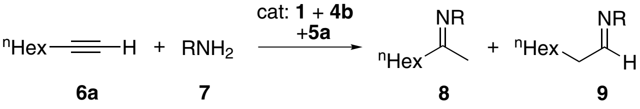
[a] Conditions: toluene, 100 °C, 2 h (40 h for run 10, 52 h for run 14, 20 h for run 15); **7**/**6** = 3; **1**(10 mol %)/**4b**/**5a** = 1/2/1.

[b] Determined by GC and NMR after hydrolysis to the ketone or aldehyde.

Intermolecular hydroamination of various alkynes **6** with aniline was tested using the three-component system of **1**, **4b**, and **5a** (Table 2).[10] Terminal alkynes having *n*-alkyl chains, **6a**–**6c**, gave the Markovnikov products, **8a**–**8c**, in nearly quantitative yields, wherein the possible *anti*-Markovnikov products, **9a**–**c**, were not detected (runs 1–3). The present system apparently changed the reactivity and regioselectivity, though the preferential formation of **8b** over **9b** (75/25 ~ 65/35) was reported with catalyst **1** alone.[11] The product yields decreased as the primary alkyl groups of **6** were substituted by secondary and tertiary groups, but the high regioselectivity was not diminished (runs 4 and 5). While alkynes **6f** and **6g** gave the expected products **8f** and **8g** in moderate yields (runs 6 and 7), trimethylsilyloxymethyl and diethylaminomethyl substituents were not tolerated under the reaction conditions (runs 8 and 9). Imine **8j** was formed in 57% yield from aliphatic internal alkyne **6j** (run 10). The reactivity of aromatic terminal alkynes, **6k**–**m**, was very sensitive to the substituents of the aromatic ring. Thus, the product yield from 4-chlorinated alkyne **6m** was only 32%, and in contrast, it increased to 85% by the 4-methyl substituent (runs 11–13). Aromatic internal alkynes **6n** and **6o** gave the products **8n** and **8o** in 85% and 89% yields, respectively. It is noteworthy that nearly perfect Markovnikov selectivity was maintained for all unsymmetrical alkynes **6** irrespective of their product yields.

Next, the reaction of 1-octyne (**6a**) with various amines **7** was carried out using **1**, **4b**, and **5a** (Table 3).[10] In the reaction with aniline derivatives, both electron-donating and -withdrawing substituents gave good results, except

Table 3. Reaction of 1-octyne with various amines[a]



Run	Amine **7**	R	Product **8**, **9**	Total yield[b] (%)	Ratio of **8**:**9**[b]
1	**7p**	4-MePh	**8p**, **9p**	85	>99:1
2	**7q**	4-MeOPh	**8q**, **9q**	92	>99:1
3	**7r**	4-FPh	**8r**, **9r**	93	>99:1
4	**7s**	4-ClPh	**8s**, **9s**	49	>99:1
5	**7t**	4-BrPh	**8t**, **9t**	94	97:3
6	**7u**	3,5-Cl_2Ph	**8u**, **9u**	53	67:33
7	**7v**	2,6-Et_2Ph	**8v**, **9v**	81	>99:1
8	**7w**	2,6-$^{i}Pr_2$Ph	**8w**, **9w**	32	97:3
9	**7x**	2,4,6-Me_3Ph	**8x**, **9x**	92	>99:1
10	**7y**	^{n}Pen	**8y**, **9y**	50	>99:1
11	**7z**	*c*-C_6H_{11}	**8z**, **9z**	33	>99:1
12	**7α**	^{t}Bu	**8α**, **9α**	23	>99:1

[a] Conditions: toluene, 100 °C, 2 h; **7**/**6** = 3; **1** (10 mol %)/**4b**/**5a** = 1/2/1.

[b] Determined by GC and NMR after hydrolysis to the ketone or aldehyde.

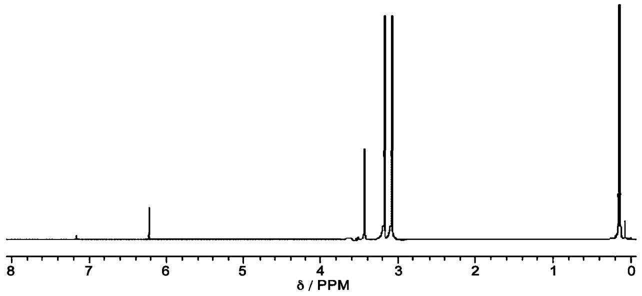


Figure 1. ^{1}H NMR of the three-component system of **1**, **4a**, and **5a** (C$_6$D$_6$).

for 4-chloroaniline (**7s**) and 3,5-dichloroaniline (**7u**) (runs 1–6). The reason for the low efficiency of **7s** and **7u** is unclear at present. Sterically demanding amines like **7v** and **7x** afforded the Markovnikov products, **8v** and **8x**, in high yields together with no or very little amounts of the other isomers **9v** and **9x**, whereas the 2,6-diisopropyl group of **7w** disturbed the reaction (runs 7–9). Compared to the original reaction with **1** alone,[11] the three-component system improved the reactivity of aliphatic amines, **7y–α**, to a certain extent, but products yields were still low and decreased in the order of $1^\circ > 2^\circ > 3^\circ$-alkyl substituents (runs 10–12). With respect to the regioselectivity, all amines **7** other than **7u** gave the Markovnikov products **8** exclusively.

We measured the NMR spectra of the three-component system to get some information on the active species generated in situ. At first, Ti-amide **1** was treated with equimolar amounts of the isolated NHCs, **4a** and **4b**, but all ^{1}H and ^{13}C NMR signals of **1** and **4** remained almost unchanged. Other titanium complexes **2** and **3** gave similar results. These observations suggest that the expected carbene complexes are not formed by this procedure, which explains the results obtained by the two-component system of **1** and **4** (Table 1, runs 2 and 3). The failure may be attributed to the four organic ligands around the Ti(IV) metal, compared to the successful examples that have at least two Cl ligands on the metal.[6] On the other hand, the ^{1}H NMR spectra of the three components of **1**, **4a**, and **5a** (1/1/1) showed a significant peak shift (Fig. 1).[12] Thus, the original signal of **1** at δ 3.08 split into two parts (δ 3.10 and 3.16) and two signals of **4a** at δ 3.76 and 7.01 moved to upper field (δ 3.43 and 6.22), respectively, together with a little downfield shift of **5a** (from δ 0.09 to 0.20). Although further work is necessary to elucidate this new species, it is likely that the NHC moiety close to the Ti metal would change the reactivity of the original **1** and realize high regioselectivity.

In summary, we have demonstrated that intermolecular hydroamination of alkynes with Ti(NMe$_2$)$_4$ (**1**) was much improved in the presence of the NHCs **4** and Li-silylamide **5a**, though the nature of the active species generated in situ is still unclear. This three-component system exhibited nearly complete Markovnikov selectivity for various kinds of alkynes and amines, irrespective of their product yields.

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10. General procedure for the reaction listed in Tables 2 and 3: all manipulations were performed under argon using standard Schlenk and vacuum line techniques. Toluene solutions (1 mL each) of NHC **4b** (91 mg, 0.3 mmol) and Li-silylamide **5a** (25 mg, 0.15 mmol) were added to the Ti-amide **1** (33 mg, 0.15 mmol), and the mixture was stirred for 1 h at room temperature. A mixture of alkyne **6** (1.5 mmol) and amine **7** (4.5 mmol) in toluene (0.5 mL) was added to the mixture, and stirring was continued for 2 h at 100 °C. The reaction mixture was passed through Florisil with ether eluent and concentrated in vacuo. GC confirmed formation of the imine products in comparison with authentic samples separately prepared. Then, the mixture was hydrolyzed to ketone or aldehyde by treatment with silica gel in aqueous toluene at room temperature overnight. After addition of dimethyl terephthalate as an internal standard, the mixture was worked-up and concentrated in vacuo. Identification of the carbonyl compounds and determination of their yields were done by GC, GC–MS, and ^{1}H NMR.
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