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Controlling selectivity: from Markovnikov to anti-Markovnikov hydroamination of alkynes

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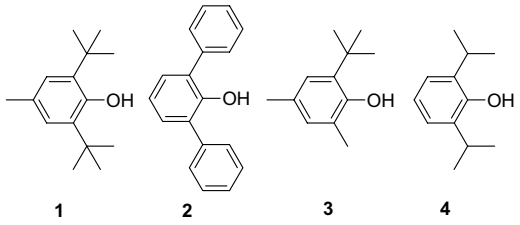
Abstract—Depending on the catalyst a remarkable control of regioselectivity is achieved for the titanium-catalyzed intermolecular hydroamination of various alkynes. Proper choice of sterically hindered phenol ligands such as **1** and **4** enables a selectivity switch from the Markovnikov to the anti-Markovnikov products from M:anti-M = > 90:10 to > 10:90.

The addition of nitrogen and oxygen compounds across carbon–carbon multiple bonds continues to be an important subject for organic synthesis and catalysis.[1] In general, these processes are perfectly suited to fulfill today's need of green chemistry because of availability of substrates, and 100% atom efficiency. By using unsymmetrical olefins or alkynes the addition reaction can lead to two isomeric products. Typically, most of the electrophilic addition reactions follow the Markovnikov rule, in which the branched compound is mainly produced. However, often the linear isomer is a desired product for industrial applications, which needs an anti-Markovnikov functionalization. Although major advances have been made in the last decades in a number of functionalization reactions, for example, hydroformylation, hydrocarboxylation, hydrocyanation, by the introduction of tailor-made transition metal complexes, still significant challenges exist with respect to control of selectivity. Clearly, control of selectivity is an important basis for application and further innovations in organic synthesis.

For some time we have been involved in the development and exploration of new methods for selective amination of olefins and alkynes. Apart from carbonylative amination (hydroaminomethylations) of olefins,[2] the direct hydroamination of alkynes attracted our interest. Among the different catalysts[3] known for alkyne hydroaminations, especially titanium complexes have found widespread interest due to their reactivity and availability. Important progress in the intermolecular hydroamination of alkynes with titanium complexes has been reported by Bergman and co-workers,[4] Doye and co-workers,[5] Odom and co-workers,[6] us,[7] and others.[8] Here, we report that by addition of different phenol ligands to $Ti(NEt_2)_4$ the regio- and chemo-selectivity of hydroaminations of terminal alkynes can be controlled. A remarkable selectivity switch from the usual Markovnikov to the anti-Markovnikov product is obtained by slightly varying the ligand structure.

Recently, we have discovered that bis(2,6-di-*tert*-butyl-4-methylphenoxo)-bis(dimethylamido)titanium catalyzes the selective Markovnikov hydroamination of terminal alkynes.[9] The easy handling, stability, and generality of the catalyst system stimulated further work using other aryloxotitanium complexes for this type of reaction. With regard to practicability we formed the corresponding aryloxotitanium complexes in situ from commercially available $Ti(NEt_2)_4$ and phenols **1**–**4** (Scheme 1).



Scheme 1. Aryloxo ligands for titanium-catalyzed amination of alkynes.

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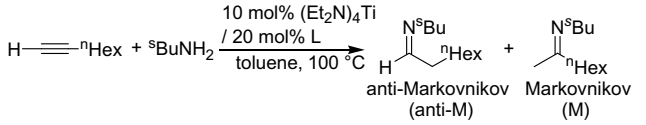
Table 1. Intermolecular hydroamination of 1-octyne with *sec*-butylamine using $(Et_2N)_4Ti$ and ligand **1**–**4**[a]



Entry	Ligand	Conversion (%)	Yield[b] (%)	Anti-M:M ratio[c]
1	**1**	100	98	10:90
2	**2**	100	97	49:51
3	**3**	100	88	72:28
4	**4**	100	97	94:6

[a] Reaction conditions: 1.5 mmol 1-octyne, 1.8 mmol amine, 10 mol% catalyst, Ti/L = 1:2, 2 mL toluene, 100 °C, 24 h.
[b] Yield is determined by GC analysis with dodecane or hexadecane as internal standard, reaction conditions are not optimized.
[c] GC analysis is used to determine the ratio of regioisomers.

In the first experiments, the addition of *sec*-butylamine to 1-octyne was studied as a model reaction (Table 1).[10] In general, the hydroamination was run in toluene at 100 °C in the presence of 10 mol% of $Ti(NEt_2)_4$, and 20 mol% of the corresponding phenol. It is important to note that only sterically hindered phenols show significant catalyst activity. By employing simple phenol or cresols as ligand no activity is observed due to the formation of stable tris- and tetrakisphenoxy titanium complexes. However, in agreement with our previous studies the use of bulky 2,6-di-*tert*-butyl-4-methylphenol **1** gave an excellent yield (98%) and a high Markovnikov selectivity (anti-M/M = 10:90). When using 2,6-diphenylphenol **2** to our surprise the selectivity significantly dropped and a 1:1-mixture of regioisomers is obtained. In the presence of 4,6-dimethyl-2-*tert*-butylphenol **3** the anti-Markovnikov product becomes the major regioisomer (anti-M/M = 72:28), and an excellent anti-Markovnikov selectivity (94:6) is obtained using 2,6-diisopropylphenol **4** as ligand. Apparently, it is possible by slight changes of the ligand structure to reverse the regioselectivity of the amination reaction, a phenomenon which has been rarely observed until today. Because of the very similar steric and electronic nature of **1** and **4** the origin of this unusual selectivity shift is not yet clear.

Next, we were interested in the generality of the observed effect (Tables 2 and 3). Hence, the behavior of ligands **1** and **4** was tested in the reaction of 1-octyne with other aromatic (aniline) and aliphatic amines (benzylamine, *n*-butylamine, *sec*-butylamine, *tert*-butylamine, cyclooctylamine). In all catalytic reactions a slight excess of amine (1.2 equiv) was employed in order to suppress oligomerization and polymerization of the alkynes. Nevertheless, in some cases small amounts of aminated dimers, oligomers, and polymers of the alkyne are observed. As shown in Table 2 the hydroamination of 1-octyne proceeds in all cases with good to excellent yield (72–99%), except for *tert*-butylamine, which is less reactive because of the steric hindrance. With aliphatic amines ligand **4** gave the corresponding anti-Markovnikov imines in good to very good regioselectivity (anti-Markovnikov/Markovnikov = 86:14 up to 99:1).

Table 2. Intermolecular hydroamination of 1-octyne with different amines using $(Et_2N)_4Ti$ and ligand **1** in comparison with ligand **4**[a]

Entry	Ligand	Amine	Conv. (%)	Yield[b] (%)	Anti-M:M ratio[c]
1	**1**	Benzylamine	100	99	20:80
2	**4**	Benzylamine	100	72	86:14
3	**1**	*n*-Butylamine	100	99	25:75
4	**4**	*n*-Butylamine	100	82	92:8
5	**1**	*sec*-Butylamine	100	98	10:90
6	**4**	*sec*-Butylamine	100	97	94:6
7[d]	**4**	*sec*-Butylamine	100	98	94:6
8[e]	**4**	*sec*-Butylamine	97	95	94:6
9	**1**	Cyclooctylamine	100	99	14:86
10	**4**	Cyclooctylamine	100	94	94:6
11	**1**	*tert*-Butylamine	50	50	74:26
12[f]	**1**	*tert*-Butylamine	75	58	88:12
13	**4**	*tert*-Butylamine	54	44	99:1
14	**1**	Aniline	100	99	22:78
15[f]	**1**	Aniline	100	96	20:80
16	**4**	Aniline	100	86	34:66

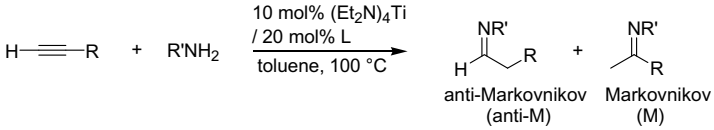
[a] Reaction conditions: 1.5 mmol 1-octyne, 1.8 mmol amine, 10 mol% catalyst, Ti/L = 1:2, 2 mL toluene, 100 °C, 24 h, reaction conditions are not optimized.
[b] Yield is determined by GC analysis with dodecane or hexadecane as internal standard.
[c] GC analysis is used to determine regioisomers.
[d] 85 °C.
[e] 5 mol% catalyst, 1 mL toluene.
[f] Ti:L = 1:1.

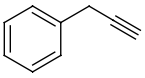
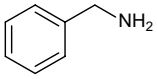
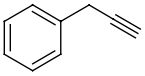
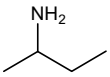
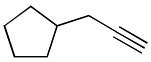
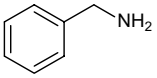
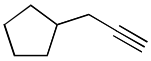
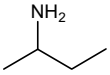
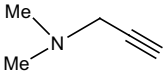
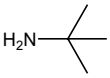
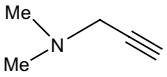
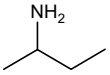
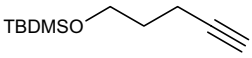
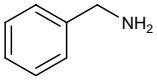
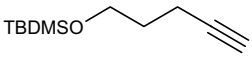
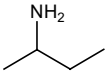
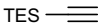
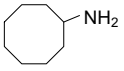
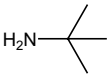
On the other hand the use of ligand **1** led preferentially to the formation of Markovnikov imines, albeit with somewhat lower selectivity. Applying aniline, both in the presence of **1** and **4** the Markovnikov isomer is obtained preferentially. In this respect it is interesting to note that recent theoretical investigations demonstrated, that electrostatic stabilization favors the Markovnikov performance for aromatic amines.[7a]

Furthermore we explored the scope of ligands **1** and **4** in hydroaminations of other alkynes. Here, we have tested the reaction of various aliphatic, aromatic, and functionalized terminal alkynes with different aryl and alkyl amines (Table 3). In most cases high conversion of the alkyne and good yield of the imines are observed. Again, except for sterically very hindered substrates, ligands **1** and **4** gave the corresponding products in opposite regioselectivity.

For example, good yield and excellent anti-Markovnikov selectivity are obtained in the reaction of 1-phenyl-3-propyne or 3-cyclopentyl-1-propyne with benzylamine and *sec*-butylamine using **4** (Table 3, entries 1–4). Sterically hindered *tert*-butylamine reacted only slowly with *N,N*-dimethylpropargylamine to give exclusively the anti-Markovnikov product using both ligands **1** and **4** (Table 3, entry 5). However, sterically less hindered amines such as *sec*-butylamine reacted fas-

Table 3. Intermolecular hydroamination of functionalized terminal alkynes with different amines using $(Et_2N)_4Ti$ and ligand **1** in comparison with ligand **4**[a]



Entry	Alkyne	Amine	Ligand	Conversion (%)	Yield[b] (%)	Anti-M:M ratio[c]
1			**1**	100	83	33:67
			4	100	74	92:8
2			**1**	100	97	32:68
			4	100	96	96:4
3			**1**	100	91	10:90
			4	100	71	80:20
4			**1**	100	97	5:95
			4	100	96	95:5
5			**1**	65	37	99:1
			4	100	66	99:1
6			**1**	100	90	36:64
			4	99	73	98:2
7			**1**	100	85	13:87
			4	100	70	75:25
8			**1**	100	98	16:84
			4	100	92	95:5
9			**1**	58	43	97:3
			4	100	93	98:2
10			**1**	12	10	99:1
			4	98	98	99:1

[a] Reaction conditions: 1.5 mmol alkyne, 1.8 mmol amine, 10 mol% catalyst, Ti/L = 1:2, 2 mL toluene, 100 °C, 24 h, reaction conditions are not optimized.
[b] Yield is determined by GC analysis with hexadecane as internal standard.
[c] GC analysis is used to determine the ratio of regioisomers.

ter with *N,N*-dimethylpropargylamine leading to the Markovnikov or anti-Markovnikov product depending on the ligand (Table 3, entry 6). Also reactions of alkynes containing protected hydroxy groups with benzylamine or *sec*-butylamine gave good to excellent yield (70–98%) and regioselectivity depending on the ligand **1** (Markovnikov) and **4** (anti-Markovnikov) (Table 3, entries 7 and 8). In addition, the hydroamination of triethylsilylacetylene with cyclooctylamine or *tert*-butylamine in the presence of **4** proceeded with very good anti-Markovnikov selectivity and yield (Table 3, entries 9 and 10).

In conclusion, we presented a general titanium-catalyzed hydroamination of terminal alkynes in the presence of different sterically hindered phenoxy ligands. The reactions can be easily performed and proceed with high yield. Depending on the ligand (**1** or **4**) the Markovnikov or the anti-Markovnikov regioisomer is formed with good to excellent selectivity. Such a control of regioselectivity has been rarely observed so far and provides an important basis for further applications of this chemistry.

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Chemischen Industrie (FCI). We thank Mrs. C. Mewes, Mrs. H. Baudisch, Mrs. A. Lehmann, and Mrs. S. Buchholz (all IfOK) for their excellent technical and analytical support.

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10. *Preparative procedure for hydroamination*: In an Ace-pressure tube under an argon atmosphere ligand **4** (2.2 mmol) was dissolved in 7.5 mL toluene. To this solution *sec*-butylamine (13.5 mmol), 1-octyne (11.3 mmol), and $Ti(NEt_2)_4$ (1.1 mmol) were added. The pressure tube was fitted with a Teflon cap and heated at 100 °C for 24 h in an oil bath. Afterwards all volatiles were removed in vacuo and distillation in vacuo afforded *sec*-butyl-octylidene-amine as a colorless oil. Isolated yield: 1.45 g (70%); bp 41–43 °C/0.1 mbar. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.57 (t, J = 5.2 Hz, 1H), 2.88 (sext, J = 6.5 Hz, 1H), 2.20 (m, 2H), 1.46 (quint, J = 7.5 Hz, 4H), 1.17–1.35 (m, 8H), 1.11 (d, J = 6.3 Hz, 3H), 0.85 (m, 3H), 0.76 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 162.9, 67.9, 35.7, 31.7, 30.4, 29.2, 29.0, 26.4, 22.6, 22.4, 14.0, 11.0. MS (EI, 70 eV) *m/z* (rel. intensity): 183 (1) [M^+], 154 (38) [$M^+ - C_2H_5$], 112 (24), 99 (100) [$C_7H_{15}^+$], 84 (44), 71 (15), 57 (50) [$C_4H_9^+$]), 44 (52), 41 (75), 29 (47). FT IR (neat, cm^{-1}): 1669 (C=N). HRMS Calcd. for $C_{12}H_{25}N$: 183.19870. Found: 183.19762.