C–H Activation

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A 2,6-Bis(phenylamino)pyridinato Titanium Catalyst for the Highly Regioselective Hydroaminoalkylation of Styrenes and 1,3-Butadienes**

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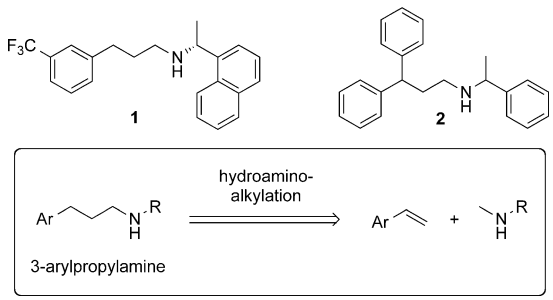
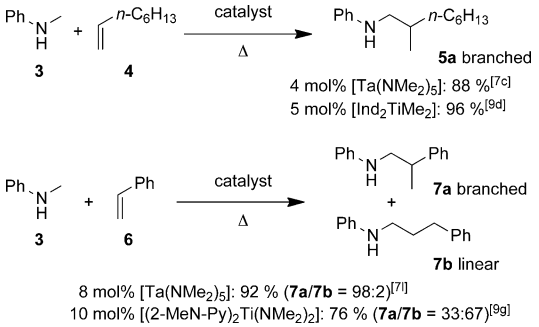
Abstract: *The C–C bond forming catalytic hydroaminoalkylation of terminal alkenes, 1,3-dienes, or styrenes allows a direct and highly atom efficient (100%) synthesis of amines which can result in the formation of two regioisomers, the linear and the branched product. We present a new titanium catalyst with 2,6-bis(phenylamino)pyridinato ligands for intermolecular hydroaminoalkylation reactions of styrenes and 1-phenyl-1,3-butadienes that delivers the corresponding linear hydroaminoalkylation products with excellent regioselectivities.*

Owing to the fact that nitrogen-containing molecules often possess highly important biological activities, amines are undoubtedly among the most important synthetic target molecules in the agrochemical, fine chemical, and pharmaceutical industries.[1] As a consequence, the development of efficient synthetic methods for the production of amines is a research area of general importance. Although the structural diversity of amines is immense, it is at least partly possible to identify privileged substructures which often cause high biological activity. For example, the calcimimetic agent cinacalcet (**1**)[2] and the calcium channel blocker fendiline (**2**)[3] shown in Scheme 1 both contain a 3-phenylpropylamine unit as a joint structural element. A highly attractive strategy for the synthesis of amines possessing a 3-arylpropylamine substructure which does not lead to the formation of any side products is shown in Scheme 1. The corresponding retrosynthetic approach relies on a metal-catalyzed hydroaminoalkylation[4–9] of widely available vinyl arenes with easily accessible *N*-methylamines that takes place under C–H bond activation in the position α to a nitrogen atom. However, in this case, it is essential that the starting materials react regioselectively to form the desired linear hydroaminoalkylation product. Hydroaminoalkylation reactions of alkenes and styrenes can be achieved in the presence of ruthenium,[5] iridium,[6] Group 5 metal,[7] zirconium,[8] or titanium catalysts[9] but the use of ruthenium and iridium catalysts is limited to amine substrates with a directing 2-pyridinyl substituent bound to the nitrogen atom of the amine. While in the presence of tantalum or titanium catalysts, terminal alkenes, such as 1-octene (**4**) or styrene (**6**), could already be converted into the branched hydroaminoalkylation products **5a** or **7a** with high regioselectivities (Scheme 2),[7,9d] corresponding



Scheme 1. Calcimimetic agent cinacalcet (**1**), calcium channel blocker fendiline (**2**), and retrosynthetic analysis of 3-arylpropylamines.



Scheme 2. Regioselectivity of the intermolecular hydroaminoalkylation of 1-octene (**4**) and styrene (**6**) with *N*-methylaniline (**3**) achieved with selected Group 4 and 5 metal catalysts (Ind = η^5-indenyl).[7c,l,9d,g]

attempts to selectively synthesize the linear regioisomers have only met with limited success. However, very recently, we presented the aminopyridinato titanium complex [(2-MeN-Py)$_2$Ti(NMe$_2$)$_2$] (Py = pyridyl)[9g] as the first example of a catalyst that favors the formation of linear hydroaminoalkylation products. For example, with this catalyst, the hydroaminoalkylation of styrene (**6**) with *N*-methylaniline (**3**) takes place with a regioselectivity of 67:33 in favor of the biologically interesting linear 3-phenylpropylamine product **7b**.

To achieve hydroaminoalkylation reactions of styrenes with improved regioselectivities in favor of the biologically interesting linear products we subsequently performed a study directed towards a structural optimization of the

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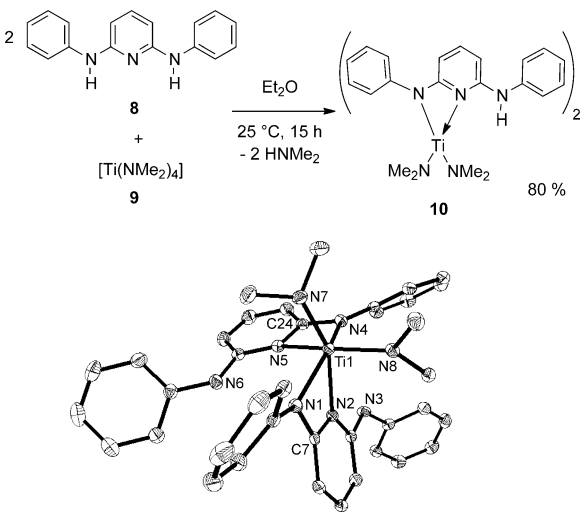
aminopyridinato ligands of the titanium catalyst. During this investigation, we found that the easily accessible titanium complex **10** (Scheme 3) with two 2,6-bis(phenylamino)pyridinato ligands is an outstandingly suitable catalyst for the



Scheme 3. Synthesis (top) and X-ray crystal structure (bottom) of complex **10**.[11] Selected bond lengths [Å] and angles [°]: Ti1-N1 2.1405(14), Ti1-N2 2.2193(14), Ti1-N4 2.0963(14), Ti1-N5 2.112(15), Ti1-N7 1.8970(14), Ti1-N8 1.9260(15); N1-Ti1-N2 60.89(5), N4-Ti-N5 61.42(5), C7-N1-Ti1 96.22(10), C7-N2-Ti1 92.78(10), C24-N4-Ti1 97.89(10), C24-N5-Ti1 93.36(10).

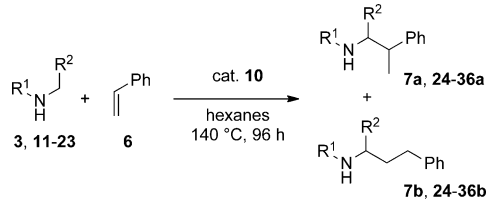
highly regioselective conversion of styrenes into the linear hydroaminoalkylation products, a transformation that has never been reported before with simple amines.

The new catalyst **10** was synthesized in 80% yield as an orange solid by treatment of $[Ti(NMe_2)_4]$ (**9**) with the easily accessible ligand precursor **8** in diethyl ether.[10] Subsequently, orange-red crystals of **10** suitable for X-ray single-crystal analysis were obtained by fast evaporation of a diluted solution of **10** in diethyl ether. The solid-state structure of **10** (Scheme 3)[11] reveals a distorted octahedral geometry around the titanium center and shows that the phenyl groups of both ligands are twisted differently out of the corresponding pyridine plane. In addition, the Ti–N bonds to the pyridine nitrogen atoms were found to be significantly longer than those to the aniline nitrogen atoms.

Fortunately, complex **10** could already be used successfully in an initial hydroaminoalkylation experiment as a catalyst for the alkylation of *N*-methylaniline (**3**) with styrene (**6**) performed under usually applied conditions (5 mol% **10**, hexanes (mixture of isomers), 140°C, 96 h, sealed Schlenk tube, Table 1, entry 1).[12,13] Most importantly, in this case, the linear regioisomer **7b** was obtained as the sole product in 81% yield after a typical work-up procedure. In addition, GC analysis performed prior to chromatographic purification of the reaction mixture confirmed the excellent regioselectivity of the hydroaminoalkylation in favor of the linear product **7b** (selectivity **7a**/**7b** = 6:94).

To investigate the scope of the new process, we subsequently performed additional hydroaminoalkylation reac-

Table 1: Hydroaminoalkylation of styrene (**6**) with various secondary amines.[13]



Entry	Amine	**10** [mol%]	Product	Yield [%][a]	Selectivity **a**/**b**[b]
1	**3**	5	**7b**	81 (**7b**)	6:94
2	**11**	5	**24b**	73 (**24b**)	5:95
3	**12**	5	**25b**	74 (**25b**)	5:95
4	**13**	5	**26b**	72 (**26b**)	6:94
5	**14**	5	**27b**	31 (**27b**)	6:94
6	**15**	5	**28b**	23 (**28b**)	5:95
7	**16**	5	**29b**	74 (**29b**)	5:95
8	**17**	10	**30b**	46 (**30b**)	6:94
9	**18**	10	**31b**	33 (**31b**)	1:99
10	**19**	10	**32b**	87 (**32b**)	5:95
11	**20**	10	**33b**	39 (**33b**)	1:99
12	**21**	10	**34b**	65 (**34b**)[c,d]	4:96
13	**22**	10	**35b**	66 (**35b**)[c,e]	1:99
14	**23**	10	**36b**	28 (**36b**)[c,d]	15:85

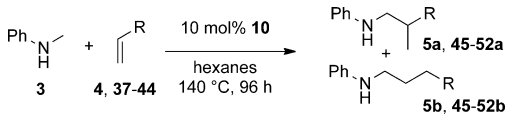
[a] Reaction conditions: amine (2.0 mmol), styrene (**6**, 313 mg, 3.0 mmol), **10** (66 mg, 0.1 mmol, 5 mol% or 131 mg, 0.2 mmol, 10 mol%), hexanes (1.0 mL), 140°C, 96 h. Yields refer to the yield of the isolated linear product **b**. [b] GC analysis prior to chromatography. [c] The product was isolated after derivatization as the corresponding *para*-toluenesulfonamide. [d] The reaction took place at the methyl group of the amine exclusively. [e] The reaction took place at the benzyl position of the amine exclusively.

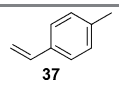
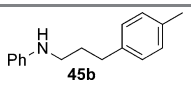
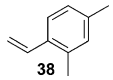
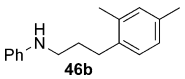
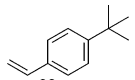
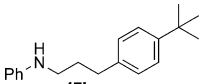
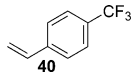
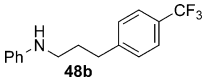
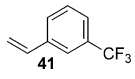
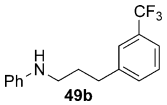
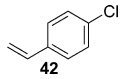
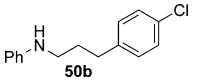
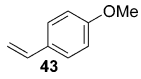
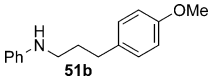
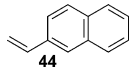
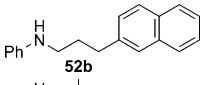
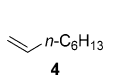
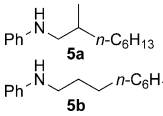
tions of styrene (**6**) with various secondary amines (Table 1). These experiments revealed that the efficiency of the reaction catalyzed by **10** is strongly influenced by the steric bulk of the amine. While the sterically less-hindered *para*- and *meta*-substituted *N*-methyltoluidines **11** and **12** selectively gave the desired linear hydroaminoalkylation products **24b** and **25b** in yields of 73% and 74%, respectively (Table 1, entries 2 and 3), *N*-methyl-*ortho*-toluidine was found to be completely unreactive under the reaction conditions. In analogy, *N*-ethylaniline (**18**) which is sterically more demanding than *N*-methylaniline (**3**) gave the corresponding linear product **31b** only in decreased yield of 33% (Table 1, entry 9). Although for this result it was necessary to increase the catalyst loading to 10 mol% it should be noted that the regioselectivity in favor of the linear isomer **31b** was excellent (99:1). In contrast to the modest reactivity of **18**, the *N*-benzyl-substituted aniline **19** delivered the linear product **32b** in very good yield (87%, Table 1, entry 10). This improved result can probably be explained by the increased reactivity of the benzylic C–H bond which becomes activated during the course of the reaction. Fortunately, the first titanium-catalyzed hydroaminoalkylation of styrene (**6**) with 1,2,3,4-tetrahydroquinoline (**20**, Table 1, entry 11) could also be achieved in the presence of 10 mol% of **10** and again, the corresponding linear product **33b** was formed exclusively. Although some of the yields obtained with **18**, **19** and **20** were only modest, the corresponding results clearly underline the fact that hydroaminoalkylation reactions can deliver products which are not accessible by hydroformylation of a styrene and a subsequent reductive amination. Reactions performed with additional *para*- and *meta*-substituted *N*-methylanilines then showed that a number of heteroatom substituents are tolerated (Table 1, entries 4–8). For example, thioether **17** as well as the electron-rich *para*-methoxy substituted substrate **16** and the electron-poor *para*-fluoro derivative **13** reacted with styrene in good to modest yields and in all cases, high regioselectivities ($\geq$94:6) in favor of the linear hydroaminoalkylation products were observed (Table 1, entries 4, 7, and 8). From a synthetic point of view, the linear product **29b** which was formed in 74% yield is particularly interesting because the *para*-methoxyphenyl group bound to the nitrogen atom is a well-established protecting group. Simple cleavage under oxidative conditions would deliver the corresponding primary amine. While the good result obtained with **13** shows that fluoro substituents are tolerated without any problems, the other halogenated substrates *para*-chloro-*N*-methylaniline (**14**) and *meta*-bromo-*N*-methylaniline (**15**) gave the linear products **27b** and **28b** only in lower yields of 31% and 23%, respectively, even though the regioselectivities remained high (Table 1, entries 5 and 6). However, despite the lower yields these results clearly demonstrate the suitability of halogenated substrates which offer the possibility of subsequent functionalization reactions. Finally, it was found that with **10** as the catalyst, even dialkylamines, such as **21**–**23**, undergo regioselective hydroaminoalkylation reactions with styrene (**6**, Table 1, entries 12–14). In these cases, the linear products which were again formed in large excess could be isolated after derivatization as the corresponding *para*-toluenesulfonamides (**34b**–**36b**) and sometimes, good yields were achieved. In this context, note that besides the catalyst $[(2\text{-MeN-Py})_2\text{Ti}(\text{NMe}_2)_2]$[9g] which was recently identified by our group, **10** is only the second titanium complex that catalyzes corresponding reactions of dialkylamines, and fortunately better regioselectivities are achieved with **10**. As observed before, reactions of the unsymmetrically substituted amines *N*-methylcyclohexylamine (**21**) and *N*-methylhexylamine (**23**) took place at the methyl group of the amine exclusively while the alkylation of *N*-methylbenzylamine (**22**) only occurred in the benzyl position.[7e,9g] During an additional experiment performed with *N*-methyl-1-(1-naphthyl)-ethylamine it was also possible to detect the selective formation of a Cinacalcet analogue (GC/MS, NMR spectroscopy) but in this case, large amounts of unconsumed starting materials prevented the isolation of the pure product.

During additional hydroaminoalkylation experiments performed with *N*-methylaniline (**3**) and various other styrenes (Table 2) it was found that in the presence of 10 mol% of **10**, many styrenes undergo highly regioselective hydroaminoalkylation reactions although the yield and the regioselectivity are strongly influenced by the steric properties of the styrene (Table 2, entries 1 and 2). While the reaction of *para*-methylstyrene (**37**) gave the linear product **45b** in good yield (74%) and with high regioselectivity (**45a**/**45b** = 9:91), a lower yield of only 42% of the linear product was obtained with the *ortho*-methyl-substituted styrene **38** and most importantly, in this case, the regioselectivity dropped dramatically to **46a**/**46b** = 33:67. Following this downward trend in reactivity, a successful reaction of a sterically more demanding *ortho*,*ortho*-dimethyl-substituted styrene could not be achieved. In contrast, the presence of a *tert*-butyl group in the *para*-position of the styrene **39** was tolerated without any problems and even the annelated benzene ring in 2-vinylnaphthalene (**44**) only resulted in a slightly reduced yield (Table 2, entries 3 and 8). Importantly, in these cases, the regioselectivities remained very high ($\geq$ 93:7) and the linear products were isolated exclusively. The results obtained with the donor- and acceptor-substituted styrenes **40**–**43** (Table 2, entries 4–7) show that both classes of substituents are generally tolerated and good yields of the corresponding linear products (**48b**–**51b**, 63–71%) can be achieved. With regard to the regioselectivity of the reaction, the electron-withdrawing CF_3 and Cl substituents lead to improved results while the electron-donating *para*-methoxy group has a negative effect. Particularly interesting is the selective formation of the linear hydroaminoalkylation product **49b** from **41** because this product contains the core structure of cinacalcet (**1**). In contrast to the behavior of styrenes, the corresponding reaction of 1-octene (**4**, Table 2, entry 9) favored the formation of the branched regioisomer **5a** and only a modest yield could be achieved. However, it must be noted that even in this case, significant amounts of the linear product **5b** were formed, a finding that is in sharp contrast to observations made with other titanium catalysts.[9d]

Because no significant polymerization of styrenes had been observed during the reactions performed with **10**, we additionally attempted hydroaminoalkylation reactions of 1-aryl-substituted (*E*)-1,3-dienes which are known to possess limited stability under harsh reaction conditions. During these

Table 2: Hydroaminoalkylation of various styrenes and alkenes with *N*-methylaniline (**3**).[13]

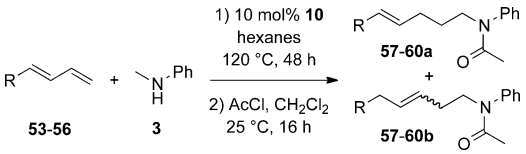


Entry	Alkene	Product	Yield [%][a]	Selectivity **a**/**b**[b]
1	 **37**	 **45b**	74 (**45b**)	9:91
2	 **38**	 **46b**	42 (**46b**)	33:67
3	 **39**	 **47b**	77 (**47b**)	6:94
4	 **40**	 **48b**	69 (**48b**)	2:98
5	 **41**	 **49b**	63 (**49b**)	2:98
6	 **42**	 **50b**	71 (**50b**)	4:96
7	 **43**	 **51b**	67 (**51b**)	11:89
8	 **44**	 **52b**	64 (**52b**)	7:93
9	 **4**	 **5a** **5b**	59 (**5a**+**5b**)[c]	89:11

[a] Reaction conditions: *N*-methylaniline (**3**, 214 mg, 2.0 mmol), alkene (3.0 mmol), **10** (131 mg, 0.2 mmol, 10 mol%), hexanes (1.0 mL), 140°C, 96 h. Yields refer to the yield of the isolated linear product **b**. [b] GC analysis prior to chromatography. [c] The yield refers to the total yield of isolated product (**a**+**b**).

studies, it was found that at 120°C in the presence of 10 mol% of **10**, successful hydroaminoalkylation of the terminal C–C double bond of the dienes **53–56** (Table 3) can be achieved with modest yields. This finding strongly underlines the high catalytic activity of **10** because to date [Ind_2TiMe_2] was the only catalyst suitable for hydroaminoalkylation reactions of 1,3-dienes.[9h] Note that in contrast to [Ind_2TiMe_2], the new catalyst **10** produces linear regioisomers almost exclusively and that the corresponding hydroaminoalkylation products were obtained as mixtures of two compounds, one with an isomerized and one with a non-isomerized C–C double bond. On the other hand, the corresponding branched products could only be detected in trace amounts by GC analysis. Owing to their better separation from residual starting materials, the products with isomerized and non-isomerized C–C double bonds[14] were isolated after conversion into their corresponding acetamides.

Table 3: Hydroaminoalkylation of (*E*)-1,3-butadienes performed in the presence of catalyst **10**.[13]



Entry	R	Yield [%][a]	Selectivity **a**/**b**[b]
1	C_6H_5 (**53**)	40 (**57a**/**57b**)	61:39
2	*p*-Me-C_6H_4 (**54**)	33 (**58a**/**58b**)	65:35
3	*p*-MeO-C_6H_4 (**55**)	34 (**59a**/**59b**)	71:29
4	*p*-Cl-C_6H_4 (**56**)	37 (**60a**/**60b**)	54:46

[a] Reaction conditions: 1) *N*-methylaniline (**3**, 214 mg, 2.0 mmol), 1,3-diene (3.0 mmol), **10** (131 mg, 0.2 mmol, 10 mol%), hexanes (1.0 mL), 120°C, 48 h; 2) acetyl chloride (1 M in CH_2Cl_2, 4.0 mmol), NEt_3 (4.0 mmol), CH_2Cl_2 (30 mL), 25°C, 16 h. Yields refer to the total yield of isolated product (**a**+**b**). [b] GC analysis prior to acetylation and chromatography.

In summary, the new titanium complex **10** was identified to be a highly efficient catalyst for the intermolecular hydroaminoalkylation of styrenes and (*E*)-1-phenyl-1,3-butadienes. With this catalyst, it is possible to obtain the corresponding linear hydroaminoalkylation products with excellent regioselectivities. This finding establishes a new and flexible synthetic approach towards the pharmaceutically important class of 3-arylpropylamines.

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[11] CCDC 988865 (**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] A detailed optimization study of the reaction conditions can be found in the Supporting Information.

[13] For experimental details, see the Supporting Information.

[14] The formation of two regioisomeric olefins was confirmed by hydrogenation of a mixture of **58a** and **58b** with Pd/C which gave the corresponding saturated derivative as the sole hydrogenation product.

