α,β-Unsaturated imines from titanium hydroamination and functionalization by rhodium C–H activation†

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Titanium pyrrolyl complexes are effective catalysts for the synthesis of α,β-unsaturated imines, which can be further functionalized using Rh-catalyzed alkene or alkyne insertion into the β-C-H bond.

Hydroamination provides an atom economical route to imines directly from alkynes.[1,2] While recent years have seen cyclopentadienyl catalysts become widely used by several groups,[3] other ancillary ligands have shown great potential.[4] We have been exploring new avenues of reactivity based on titanium catalysis. For example, catalysts for the hydroamination of alkynes with 1,1-disubstituted hydrazines, a reaction that leads to hydrazones and indoles, have been reported.[5] In addition, 3-component couplings to yield α,β-unsaturated β-iminoamines from an amine, alkyne, and isonitrile were developed where a C≡C triple bond is formally iminoaminated.[6] These types of titanium catalyzed reactions are applicable with most primary amines and most alkynes. Most functional groups are tolerated; however, some that are not include groups more acidic than the amine (*e.g.* alcohols need to be protected by silylation), some esters, and nitro groups.

The synthesis of α,β-unsaturated imines[7] by reaction of an α,β-unsaturated ketone or aldehyde with a primary amine is often complicated by competing Michael addition.[8] Barluenga and coworkers reported that HgCl₂ can be used to catalyze the addition of secondary amines and aryl-substituted primary amines to enynes where the alkyne is terminal.[9] Using titanium catalysis, we hoped to generate α,β-unsaturated imines while avoiding mercury reagents and expanding the methodology to alkyl primary amines and internal alkynes.

Pyrrolyl ligands have been of some interest because several chelating versions may be generated in a single step from commercially available compounds.[10] Addition of pyrrolyl ligands to commercially available Ti(NMe₂)₄ generates complexes active for hydroamination, which may be either isolated or used *in situ*. Recently reported are very active catalysts based on the dipyrrolylmethane framework (Chart 1) such as Ti(dmpm)(NMe₂)₂ (**1**), where dmpm is 5,5-dimethyldipyrrolylmethane.[11]

Some examples of enyne hydroamination are shown in Table 1. The amines chosen for this initial study were aniline and cyclohexylamine (CyNH₂). The regioselectivity of the reactions was quite good. In the cases described, only one regioisomer was observed and separations were readily accomplished by column chromatography and/or vacuum distillation. In most cases, amination of the alkyne α to the vinyl group was favored. Where the
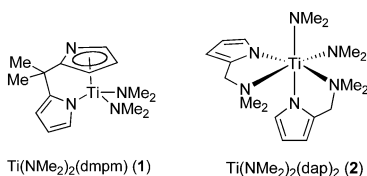
alkyne was substituted with a phenyl group, *i.e.* entries 3 and 7, amination occurred β to the vinyl substituent. These regioselectivities are somewhat unexpected considering previous work using phenylacetylene and 1-phenylpropyne as substrates, where C–N bond formation β to the phenyl group is often favored.[3–6]

For highly reactive and polymerization-sensitive enynes, *e.g.* where the alkyne is terminal, the catalyst Ti(dap)₂(NMe₂)₂ (**2**),[5] where dap is *N,N*-dimethylaminomethylpyrrolyl, was often optimal (Chart 1). While **2** was originally designed for hydrazine hydroamination catalysis, it is a mild promoter of the amine transformation that is less prone to side reactions with highly reactive substrates. Because hydroamination is sensitive to alkyne size,[5] reactions involving disubstituted alkynes, especially with less reactive alkylamines, are often better accomplished using the more reactive catalyst **1**. In addition, arylamine reactions are generally more facile and can be promoted with less active catalysts such as **2**.

An obvious application of the newly synthesized α,β-unsaturated imines would be in Diels–Alder reactions to generate 6-membered nitrogen heterocycles. However, Diels–Alder reactions with 1-aza-1,3-butadienes are often problematic[12] and reactions attempted with several dienophiles (alkynes and alkenes) and several examples of the α,β-unsaturated imines in Table 1 did not result in clean generation of the anticipated heterocycle under the conditions attempted. An alternative strategy to synthesize similar products to alkyne Diels–Alder chemistry would be to use a C–H activation/ alkyne insertion[13] reaction (Scheme 1) followed by 6-electron electrocyclization[14,15] to generate the dihydropyridine. If conditions could be found where the intermediate imine need not be isolated, the reaction would constitute an enyne, amine, and alkyne coupling to form a substituted heterocyclic product in a one-pot, tandem-catalysis sequence.

Chart 1 Titanium catalysts used in this study.

Table 1 Hydroamination of enynes to generate α,β-unsaturated imines

Entry	Amine	Enyne	Conditions[a]	Product[b] (% yield)
1	PhNH₂		B, 50 °C, 16 h	(88)
2			B, 50 °C, 44 h	(64)
3			B, 130 °C, 19 h	(70)
4	CyNH₂[c]		B, 50 °C, 24 h	(78)
5			B, 50 °C, 43 h	(73)
6			A, 100 °C, 5 h	(73)
7			A, 100 °C, 70 h	(73)

[a] A is 10 mol% Ti(dmpm)(NMe₂)₂ (**1**) in PhCl solvent, B is 10 mol% Ti(dap)₂(NMe₂)₂ (**2**) in toluene. [b] Yields are of isolated product on multigram scales. [c] Cy = cyclohexyl.

† Electronic supplementary information (ESI) available: details of the synthesis of compounds in Table 1 and Scheme 1 including analytical and spectroscopic data for new compounds. See http://www.rsc.org/suppdata/cc/b4/b405620e/
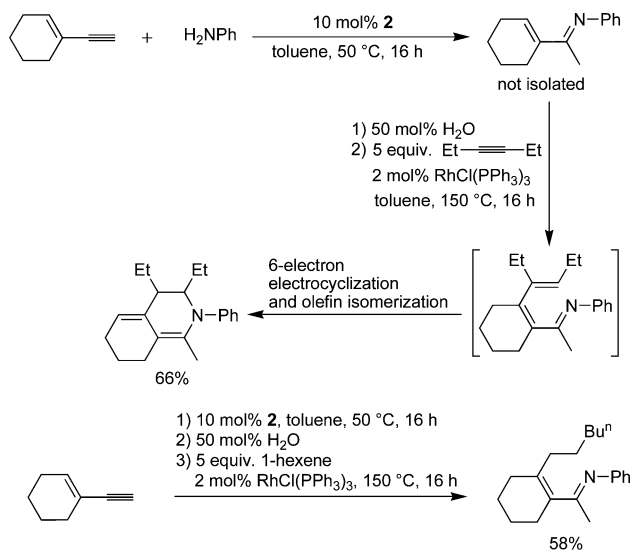
Scheme 1 Hydroamination/C–H insertion tandem catalysis examples.

Initial attempts using isolated and purified imines, *e.g.* the imine in Entry 1 of Table 1, were successful using 2 mol% Wilkinson's catalyst and 3-hexyne. Attempts to use α,β-unsaturated imines from titanium hydroamination without purification were not successful and resulted only in reisolation of the imine starting material. It was thought that the titanium catalyst might be interfering with the rhodium-catalyzed process. Consequently, 50 mol% water was added to decompose the titanium catalyst prior to addition of Wilkinson's catalyst‡ and alkyne. With the addition of water, the C–H activation/insertion reactions ran successfully without imine purification. In the presence of the rhodium catalyst, the product was apparently isomerized from the unobserved dihydropyridine that would be the result of the electrocyclization to the compound isolated. With unsymmetrical alkynes, isomeric mixtures were obtained using ClRh(PPh₃)₃ as catalyst, and further catalyst development is desirable to overcome regiochemical and other issues associated with this C–H activation methodology.§ As shown in Scheme 1, the same procedure may be used with insertion of an alkene. The reaction was found to give the anti-Markovnikov insertion product into the β-C–H bond.¶

Hydroamination of enynes using titanium catalysis is a convenient method for α,β-unsaturated imine synthesis. Preliminary investigations suggest that hydroamination may be used in combination with a C–H activation/alkyne insertion strategy to yield dihydropyridines and related products.[16]

Notes and references

‡ Attempts to use the catalyst commonly employed by Murai and coworkers for similar transformations, Ru(H)₂(CO)(PPh₃)₃, did not lead to the C–H activation product under any of the conditions attempted.

§ Reactions with diphenylacetylene under the same conditions showed no reaction with ClRh(PPh₃)₃ as catalyst. Other unsymmetrical, internal alkynes, *e.g.*, 1-phenylpropyne, reacted with good conversion of the starting material to products with the expected mass that were ~ 1 : 1 mixtures of isomers. Some cyclotrimerization products were observed with terminal alkynes, *e.g.*, 1-hexyne.

¶ The product was isolated after NaB(CN)H₃ reduction to the amine.

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