

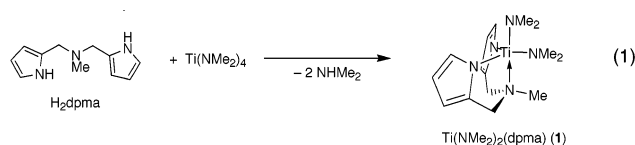
A Titanium-Catalyzed Three-Component Coupling To Generate α,β -Unsaturated β -Iminoamines

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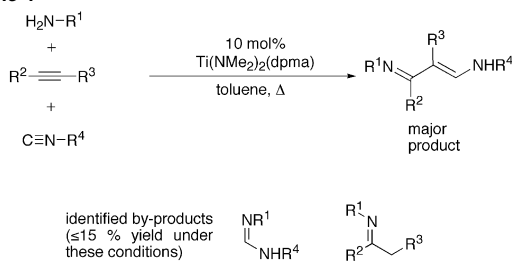
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Titanium-mediated hydroamination of alkynes by primary amines has drawn a great deal of recent interest.¹ The reactions are often rapid, regioselective, and utilize inexpensive catalysts. We have been exploring methodologies to expand the scope of titanium hydroamination catalysis to generate products outside of imines and recently published catalysts effective for the 1,1-disubstituted-hydrazine hydroamination of alkynes, which provides hydrazones and substituted indoles.² Continuing in this area, we sought to identify reactions where three molecules are coupled in a single synthetic step.³ In this report, we demonstrate that titanium catalysts are effective for three-component couplings to form α,β -unsaturated β -iminoamines.



The synthesis of pyrrolyl complex $\text{Ti}(\text{NMe}_2)_2(\text{dpma})$ (**1**), where dpma is *N,N*-di(pyrrolyl- α -methyl)-*N*-methylamine, is shown in eq 1.⁴ The H_2dpma ligand is prepared in a single, high-yielding step (70–80%) by a Mannich reaction between pyrrole, methylamine hydrochloride, and formaldehyde.^{4b} Complex **1** is available in near quantitative yield by treatment of commercially available $\text{Ti}(\text{NMe}_2)_4$ with H_2dpma . To avoid isolation of the air-sensitive complex, **1** can be generated in situ with comparable catalytic activity. Catalyst **1** has a relatively broad scope and is applicable for hydroamination of terminal and internal alkynes by alkyl and arylamines.⁵

Scheme 1



A generalized reaction is shown in Scheme 1. The major product for the substrates shown is due to three-component coupling. Two byproducts that have been identified from reaction mixtures are the *N,N'*-disubstituted-formamidine from reaction of isonitrile with the primary amine, a reaction catalyzed by several metal complexes.⁶ In some cases, the imine product from simple alkyne hydroamination is observed. However, with the substrates investigated thus far, the imine is generated in only trace quantities as analyzed by GC-FID of crude reaction mixtures.

Some representative examples of three-component coupling reactions are given in Table 1. For entries 1 and 3, the formamidine

Table 1. Examples of $\text{Ti}(\text{NMe}_2)_2(\text{dpma})$ (**1**)-Catalyzed Three-Component Couplings

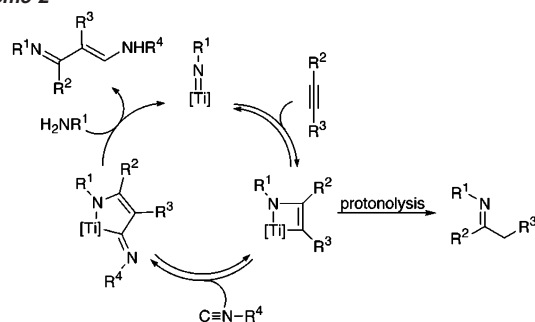
#	amine	alkyne	isonitrile	product ^b (%yield)
1	PhNH_2	$\text{Bu}^n\text{-}\equiv\text{-H}$	$\text{C}\equiv\text{N-Bu}^t$	 (77) ^d
2			$\text{C}\equiv\text{N-R}^a$	 (83)
3		$\text{Ph}\text{-}\equiv\text{-Me}$	$\text{C}\equiv\text{N-Bu}^t$	 (72) ^e
4			$\text{C}\equiv\text{N-R}$	 (57)
5	CyNH_2^c	$\text{Bu}^n\text{-}\equiv\text{-H}$	$\text{C}\equiv\text{N-Bu}^t$	 (1.2 : 1, 66)
6		$\text{Ph}\text{-}\equiv\text{-H}$	$\text{C}\equiv\text{N-R}$	 (68)

^a $\text{R} = 1,1,3,3$ -tetramethylbutane. ^b Reactions were carried out at 100 °C in toluene with 10 mol % **1** and are complete in <48 h. Products were isolated on multigram scales by column chromatography. ^c Cy = cyclohexyl. ^d 13% yield of *N,N'*-phenyl-*tert*-butylformamidine was isolated. ^e 15% yield of *N,N'*-phenyl-*tert*-butylformamidine was isolated.

byproduct was produced in sufficient quantities for isolation. Other reactions had smaller quantities of formamidine observable by GC. In most cases, 1.1 or 1.2 equiv of isonitrile was employed to compensate for formamidine generation. Other byproducts for the reactions are sometimes present in trace quantities; studies are underway aimed at isolation and structural characterization of these minor products. The desired compounds were purified and isolated on multigram scales by column chromatography. The products have multiple tautomers accessible. For most entries, the more stable tautomer, as determined by NMR spectroscopy, is shown. Entry 5b is apparently a tautomeric mixture in solution.

With **1** as catalyst, the syntheses were successful with arylamines, alkylamines, terminal alkynes, and internal alkynes with isonitriles bearing a quaternary alkyl group. Reactions with phenyl isonitrile

Scheme 2



and cyclohexyl isonitrile have not yielded three-component coupling products under the same conditions. Alternative conditions, catalysts, and isonitriles are under exploration to further expand the scope of the reaction.

A couple of control experiments are worthy of note. First, the three components do not react in the absence of catalyst, even to form the observed byproducts of the catalysis. Second, treatment of isolated imine with isonitrile in the presence of catalyst does not result in the generation of the three-component coupling product. Consequently, the reaction is not simply hydroamination followed by a catalyzed reaction with an isonitrile. Apparently, the isonitrile must be present during the C–N bond forming process to yield the α,β -unsaturated β -iminoamines.

We propose the catalysis involves the reaction of isonitrile with an intermediate in hydroamination (Scheme 2). From the established mechanism for titanium hydroamination,⁷ a titanium imido complex can react reversibly with an alkyne to form a metalazacyclobutene. Because imine does not generate a three-component coupling product under the reaction conditions (vide supra), we propose that the isonitrile insertion occurs prior to protonolysis of the metalazacyclobutene. Consequently, 1,1-insertion of an isonitrile into a Ti–C bond, which is usually favorable and reversible, generates a new C–C bond and an iminoacyl complex. Protonolysis of an iminoacyl-amido intermediate by amine would generate the observed three-component coupling product.

Regioselectivities in the three-component coupling reactions using **1** as catalyst have been similar to results expected from hydroamination. For example, hydroamination of 1-hexyne by cyclohexylamine gives a 1.6:1 mixture of Markovnikov:anti-Markovnikov products.⁵ Three-component coupling between 1-hexyne, cyclohexylamine, and *tert*-butylisocyanide (entry 5, Table 1) results in a 1.2:1 mixture of separable regioisomers. Similarly, cyclohexylamine hydroamination of phenylacetylene with **1** as catalyst provides a 1:6 Markovnikov:anti-Markovnikov isomer ratio.^{5b} Consistent with this, the major isomer generated during the three-component coupling has the nitrogen bearing the cyclohexyl group β to the phenyl group (entry 6, Table 1). The regioisomer with the phenyl α to the nitrogen bearing the cyclohexyl group was observed by GC/FID, ratio of 1:8, but was not isolated.

The products generated during these catalyses are reminiscent of β -diketimines, which in deprotonated form are common ligands for both early and late transition metals.⁸ This titanium catalysis allows access to highly unsymmetrical derivatives in a single synthetic step. In addition, 1-azabutadienes can be used in Diels–Alder reactions to form heterocycles.⁹ For example, α,β -unsaturated β -iminoamines react with ketenes to produce 3,4-dihydro-2-

pyridones.¹⁰ We are currently exploring other catalysts, the scope of this new transformation, and potential one-pot generation of heterocycles from the product 1-azabutadienes.

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Supporting Information Available: Syntheses and characterization data for products in Table 1 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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