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A Multicomponent Coupling Sequence for Direct Access to Substituted Quinolines

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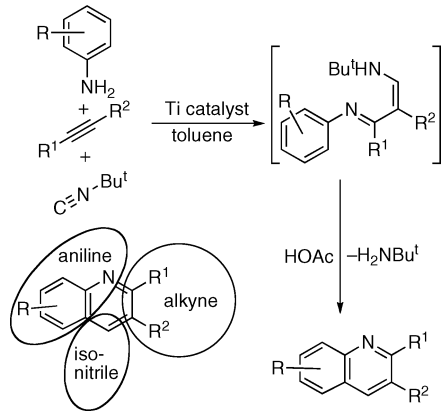
ABSTRACT



A titanium-catalyzed three-component coupling reaction can be used to generate tautomers of *N*-aryl-1,3-diimines. Simple treatment of these products with acetic acid leads to cyclization forming quinoline derivatives in a one-pot procedure. The primary amines employed can be substituted anilines, aminonaphthalenes, or even heterocyclic amines, which leads to a variety of fused-ring heterocyclic frameworks. The one-pot yields varied from 25−71% for the 18 examples presented in this study.

New synthetic protocols[1] for quinolines, due to the ubiquity of these heterocycles, are of great interest as these heterocycles[2] have utility in diverse areas such as pharmaceuticals,[3] photonic materials,[4] and redox switches.[5]

We have been investigating a titanium-catalyzed three-component coupling (3CC) reaction that generates tautomers of 1,3-diimines.[6] Here we report that these 3CC products, when prepared using aromatic amines, can be used as direct precursors for quinolines and related heterocycles in a one-pot procedure simply by adding acetic acid to the multicomponent coupling product.

The proposed catalytic cycle involved in the synthesis of the 3CC product is shown in Scheme 1 and is based on the mechanism for catalytic hydroamination.[7] It is proposed that the titanium precatalyst, bis(dimethylamido), generates a titanium imido on reaction with a primary amine. The titanium imido undergoes a [2 + 2]-cycloaddition reaction

(1) For some recent developments and examples, see: (a) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707. (b) Zhang, Z. H.; Tan, J. J.; Wang, Z. Y. *Org. Lett.* **2008**, *10*, 173. (c) Kouznetsov, V. V.; Romero Bohórquiez, A. R.; Stashenko, E. E. *Tetrahedron Lett.* **2007**, *48*, 8855.

(2) For some selected recent references on transition-metal-catalyzed synthesis of nitrogen heterocycles with emphasis on multicomponent couplings, see: (a) Ackermann, L.; Sandmann, R.; Kaspar, L. T. *Org. Lett.* **2009**, 2031. (b) Krenske, E. H.; Houk, K. N.; Arndtsen, B. A.; St. Cyr, D. J. *J. Am. Chem. Soc.* **2008**, *120*, 5510. (c) Lu, Y.; Arndtsen, B. A. *Angew. Chem.* **2008**, *47*, 5430. (d) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171. (e) Isamber, N.; Lavilla, R. *Chem.−Eur. J.* **2008**, *14*, 8444.

(3) For a review, see: Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.

(4) Zhang, X.; Shetty, A. S.; Jeneckhe, S. A. *Macromolecules* **1999**, *32*, 7422.

(5) Das, D.; Dai, Z.; Holmes, A.; Canary, J. W. *Chirality* **2008**, *20*, 585.

(6) (a) Cao, C.; Shi, Y.; Odom, A. L *J. Am. Chem. Soc.* **2003**, *125*, 2880. (b) Majumder, S.; Gipson, K. R.; Staples, R. J.; Odom, A. L. *Adv. Synth. Catal.* **2009**, *351*, 2013. (c) Banerjee, S.; Shi, Y.; Cao, C.; Odom, A. L. *J. Organomet. Chem.* **2005**, *690*, 5066. (d) For a recent study on a potential side reaction to this 3CC that can occur with some substrates, see: Barnea, E.; Majumder, S.; Staples, R. J.; Odom, A. L. *Organometallics* **2009**, 3876.

(7) For a recent review on hydroamination, see: Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

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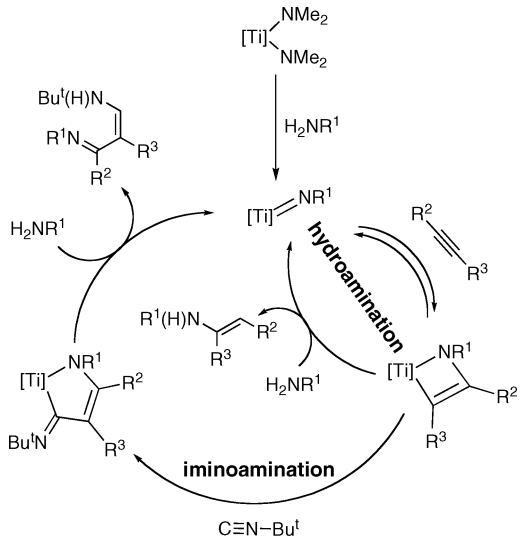
Scheme 1. Proposed Catalytic Cycles for Hydroamination and Iminoamination



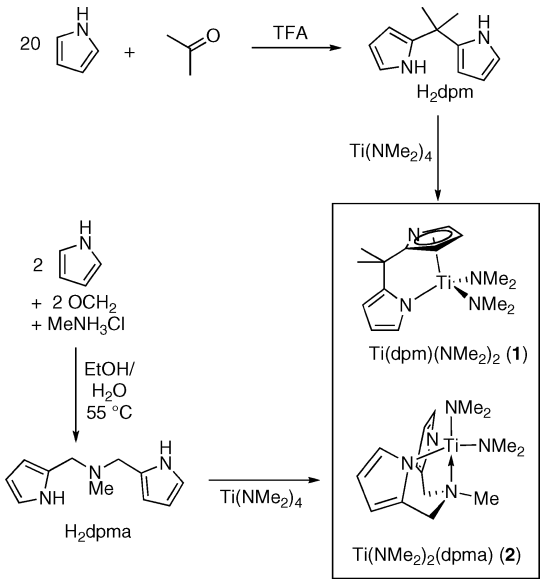
with an alkyne to obtain an azatitanacyclobutene. Isonitrile traps this Ti−C containing intermediate to form a 5-membered metallacycle,[8] which is then protolytically cleaved from the metal for catalyst turnover. The overall reaction is the addition of iminyl and amine groups across the C−C triple bond of the alkyne, iminoamination.

This new quinoline synthesis can be viewed as an alternative to some well-known quinoline syntheses that use anilines and 1,3-dicarbonyls or related compounds, such as the Combes synthesis.[9] These reactions are very effective but require somewhat difficult to access unsymmetrical 1,3-dicarbonyls if their quinolines are to be produced.[10] One of the benefits of this class of transformations is that it takes advantage of the large number of commercially available aniline derviatives.

The titanium catalysts employed here use readily prepared pyrrolyl ligands. Both of ligands can be made in a single step from pyrrole. The most commonly employed catalyst was Ti(dpm)(NMe_2)$_2$ (**1**);[11] H_2dpm is available from condensation of pyrrole and acetone (Scheme 2) in the presence of trifluoroacetic acid (TFA).[12]

An alternative catalyst advantageous for some substrates was Ti(dpma)(NMe_2)$_2$ (**2**).[13] The H_2dpma ligand was prepared[14] in a single step by Mannich condensation of pyrrole, formaldehyde, and methylamine hydrochloride in ethanol/water (Scheme 2).

Scheme 2. Generation of Titanium Catalysts



Both catalysts can either be isolated or can be generated in near-quantitative yield by in situ reaction of commercially available Ti(NMe_2)$_4$ with the protonated form of the ligand.

The results for 3CC of some arylamines followed by acid treatment with a few alkynes are shown in Table 1. The yields are modest, but the reactions are readily run on multigram scales and provide the products from a single pot. In these reactions, a small excess of the *tert*-butyl isonitrile was added.

The cyclizations of the 3-CC product involve Brönsted acid-catalyzed[15] intramolecular electrophilic attack on the pendant aromatic ring. Then, *tert*-butyl amine is lost in the aromatization of the nitrogen heterocycle.

Using this methodology, the 4-position of the quinoline product will be unsubstituted. In addition, the route takes advantage of the abundance of arylamines available commercially to make substituted quinolines.

The regioselectivity of the reaction would be set by the [2 + 2]-cycloaddition reaction in conjunction with the relative trapping rates by isonitrile under this scheme. It has been proposed that the regioselectivity of the addition is electronically controlled when an arene is found in the alkyne by stabilization of a partial anionic charge adjacent to the metal in the azametallacyclobutene intermediate.[16] This

(8) For a recently characterized example of the proposed 5-membered metallacyclic intermediates prepared by isonitrile insertion, see: Vujkovic, N.; Fillol, J. L.; Ward, B. D.; Wadepohl, H.; Mountford, P.; Gade, L. H. *Organometallics* **2008**, *27*, 2518.

(9) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141.

(10) For a recent quinoline synthesis involving rhodium catalysis, see: Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117.

(11) (a) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chem. Commun.* **2003**, 586. (b) Novak, A.; Blake, A. J.; Wilson, C.; Love, J. B. *Chem. Commun.* **2002**, 2796.

(12) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391.

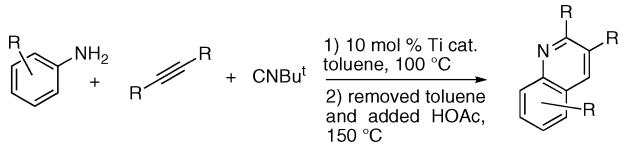
(13) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2001**, *40*, 1987.

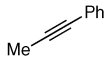
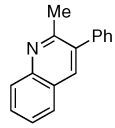
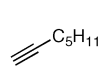
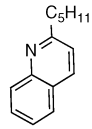
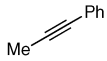
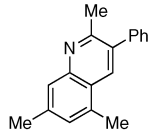
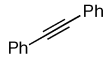
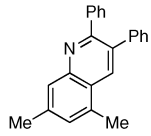
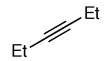
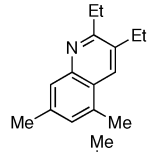
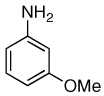
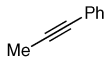
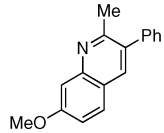
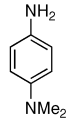
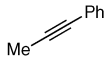
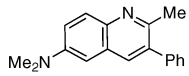
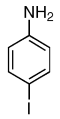
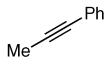
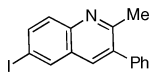
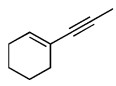
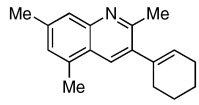
(14) Li, Y.; Turnas, A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2002**, *41*, 6298.

(15) A related acid-catalyzed cyclization of 1,3-diimine tautomers has been used previously to generate quinolines in a multistep synthesis. Their 1,3-diimine tautomers were prepared from enolizable arylimine condensation with nitriles. The cyclization was accomplished by addition of the Lewis acid $AlCl_3$. Barluenga, J. Cuervo, H. Fustero, S. Gotor, V. *Synthesis* **1987**, 82. Attempts to use $AlCl_3$ with the derivatives listed here resulted in very low yields.

(16) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753.

Table 1. Examples of Quinoline Syntheses

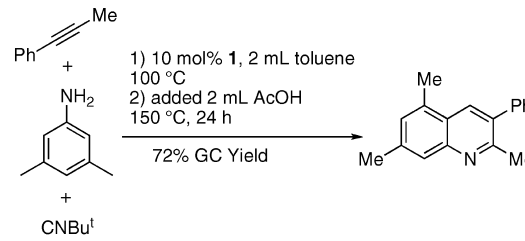


	amine	alkyne	catalyst	product	%yield[a]
1			**1**		55
2			**2**		30
3			**1**		71
4			**1**		30[b]
5			**1**		36
6			**1**		54
7			**1**		50
8			**1**		25
9			**1**		40

[a] Most reactions carried out with arylamine, alkyne, and *tert*-butyl isonitrile in a 1:1:1.5 ratio with 10 mol % catalyst at 100 °C for 24−48 h. Once the 3CC is complete, product was heated at 150 °C in HOAc. [b] Used 20 mol % of Ti(dpm)$(NMe_2)_2$ at 140 °C.

results in 3-aryl substitution being electronically favored for aryl-substituted alkynes. For 1-hexyne, the favored product was generally the 2-substituted quinoline derivative.

For the majority of the reactions done here, the 3CC reaction was run in toluene, and this solvent was removed before the acid was added. However, if the solvent removal is inconvenient, the acid can be added without removal of volatiles at this intermediate stage. For substrates where this has been tried, the yield from the reaction was not affected. For example, the substrate combination in Table 1, entry 3, was used in a reaction sequence using toluene as solvent with the titanium catalyst, followed by addition of acetic acid to the reaction mixture (eq 1). In other words, the solvent system for the cyclization step was 1:1 toluene/acetic acid. The calibrated GC yield was essentially the same as running the reaction in acetic acid only.

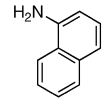
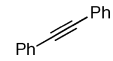
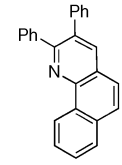
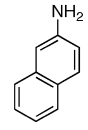
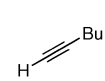
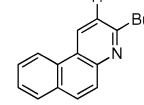
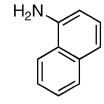
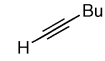
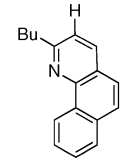
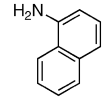
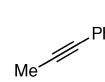


(1)

1 mmol:1 mmol:1.5 mmol

Both α- and β-aminonaphthalenes were also explored, which provide various benzoquinolines (Table 2). From this sampling, the reaction appears equally amenable to having the amine in either of these two positions (entries 2 and 3).

Table 2. Examples of Benzoquinoline Syntheses

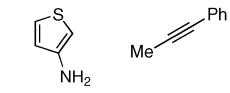
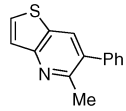
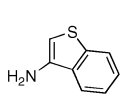
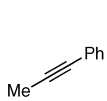
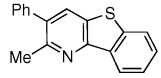
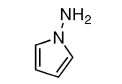
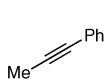
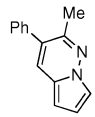
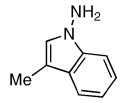
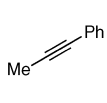
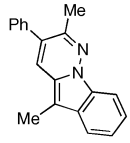
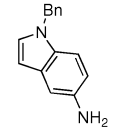
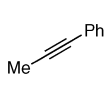
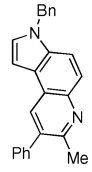
	amine	alkyne	catalyst	product	%yield[a]
1			**1**		44[b]
2			**2**		47[c]
3			**2**		60[d]
4			**1**		67

[a] Most reactions carried out with arylamine, alkyne, and *tert*-butyl isonitrile in a 1:1:1.5 ratio with 10 mol % of catalyst at 100 °C for 24−48 h. [b] Used 20 mol % **1** at 140 °C. [c] Total yield for two regioisomers; isomer shown favored 10:1. [d] Total yield for two regioisomers; isomer shown favored 2.5:1.

The reaction can also be generalized to include various amine-substituted heterocycles. The results of a short study using 1-phenylpropyne are shown in Table 3 and illustrate the variety of heterocyclic frameworks available.

Using 2-aminothiophene as a substrate generated a thienopyridine (entry 1). In addition, 3-aminobenzothiophene provided

Table 3. Examples of Products Prepared from Amino Heterocycles

	amine	alkyne	catalyst	product	%yield[a]
1			**1**		43[b]
2			**1**		45
3			**1**		37
4			**1**		31
5			**1**		56

[a] Most reactions carried out with arylamine, alkyne, and *tert*-butyl isonitrile in a 1:1:1.5 ratio with 10 mol % of catalyst at 100 °C for 24−48 h. [b] Converts directly to the product without external acid.

the benzothienopyridine (entry 2). The methodology is also applicable to pyrrolo- and indolopyridazines.

Again for these heteroarmatic amines, unsymmetrical alkynes containing an aromatic group generally result in products with the alkyne-derived aryl β to the pyridine nitrogen in the product. Alkyl groups α to the pyridine nitrogen in the product can be favored with the use of catalyst **2**.

As shown in Table 1, relatively electron-rich aromatic amine derivatives can be readily converted to quinolines using this methodology. We propose an iminium intermediate that undergoes intramolecular electrophilic aromatic substitution as the cyclization step. This is supported by observations with the electron-deficient 4-cyano-aniline as substrate. The reaction of 4-cyanoaniline, 1-phenylpropyne, and *tert*-butylisonitrile in the presence of **1** produced the expected 3CC product by GC−FID and GC−MS. However, treatment with acetic acid in an attempt to cyclize produced only a trace of the quinoline derivative. Instead, large amounts of *N*-(4-cyanophenyl)acetamide were observed as the 3CC product was consumed. This side reaction of acetamide formation from acetic acid solvent was observed with other substrates as well but was qualitatively more prevalent in systems with sluggish cyclizations.[17]

Inexpensive titanium catalysis can be used to access a variety of pyridine-related fused heterocyles in a single step from commercially available amines, alkynes, and isonitriles. Further applications of some of these heterocycles and this methodology are under development.

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Supporting Information Available: Experimental and characterization details for quinolines. ^{1}H and ^{13}C NMR spectra for the quinolines. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For examples of related observations in a similar cylization see Tom, N. J.; Ruel, E. M. *Synthesis* **2001**, 1351.