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Titanium catalyzed one-pot multicomponent coupling reactions for direct access to substituted pyrimidines

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ABSTRACT

A titanium-catalyzed 3-component coupling reaction can be used to generate tautomers of 1,3-diimines. These diimines produced in situ undergo condensation with amidines in a one-pot procedure to provide substituted pyrimidines. Seventeen examples of pyrimidines are provided using this one-pot, 4-component procedure from simple starting materials. In some cases, catalyst architecture can be tuned to control the regioselectivity of the alkyne addition. Finally, the regioselectivity of amidine addition to unsymmetrical 1,3-diimines is discussed.

1. Introduction

The pyrimidine core is found in a wide range of natural products and bioactive molecules.[1] Recently, pyrimidyl structural motifs have appeared in a variety of synthetic pharmacophores having antibacterial,[2] antimicrobial, antifungal,[3] and antimycotic[4] activities. Even in the drug zidovudine (Retrovir®), the first drug approved for the treatment of AIDS and HIV infection, is based on the pyrimidine core.[5] Some diaminopyrimidines, such as pyrimethamine (Daraprim®) or trimethoprim (Proloprim®) are powerful antimalarial drugs.[6]

The ubiquity of the pyrimidine substructure in natural products and pharmaceuticals, has resulted in a plethora of synthetic routes to this important ring system; most of these synthetic protocols involve direct condensation of amidines or amidinium salts with 1,3-dicarbonyl compounds.[7] Cross-coupling chemistry has advanced the synthesis of various substituted pyrimidines from halogen precursors.[8] In these methods the practical disadvantage is the difficulty in synthesizing unsymmetrical pyrimidine compounds due to the multistep synthesis of the unsymmetrical diketone precursors or the appropriately substituted halo pyrimidines.

To this end, transition metal catalyzed multicomponent coupling reactions can be a suitable alternative for direct access to synthetic equivalents of unsymmetrical 1,3-dicarbonyl precursors. Herein we report a new titanium mediated one-pot multicomponent coupling followed by amidine condensation sequence for direct access to substituted pyrimidines.

2. Results and discussion

In previous multicomponent coupling research in our group, we discovered a novel titanium-catalyzed 3-component (3CC) coupling[9] of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers.[10] In this work in situ generated 1,3-diimine tautomers are reacted with a variety of amidine derivatives as a new one-pot 4-component coupling strategy for direct access to substituted pyrimidine compounds.

The multicomponent reaction utilized here is a formal addition of iminyl and amine groups across an alkyne triple bond, iminoamination.[8] The proposed catalytic cycle (Scheme 1) for the formation of the 3CC product is based on the mechanism of catalytic alkyne hydroamination.[11] It is proposed that the titanium precatalyst, bis(dimethylamido)titanium, reacts with a primary amine to generate a titanium imido species, which undergoes reversible [2+2]-cycloaddition with an alkyne to generate an azametallocyclobutene intermediate.[12] Subsequent, 1,1-insertion of isonitrile into the Ti–C bond generates a five-membered metallacycle,[13] which is then proteolytically cleaved from the metal for catalyst turnover.

For this study, two pyrrole-based titanium catalysts, Ti(dpma)$(NMe_2)_2$[14] (**1**) and Ti(dpm)$(NMe_2)_2$[15] (**2**), were employed. Both these catalysts can be synthesized in a single step in almost

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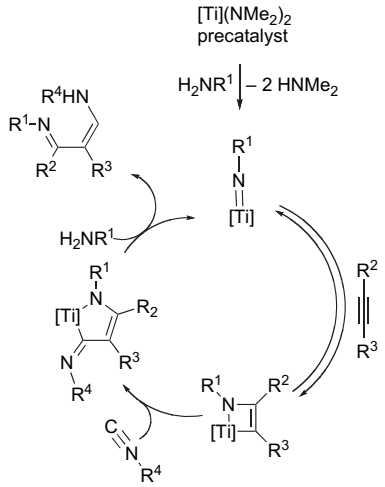
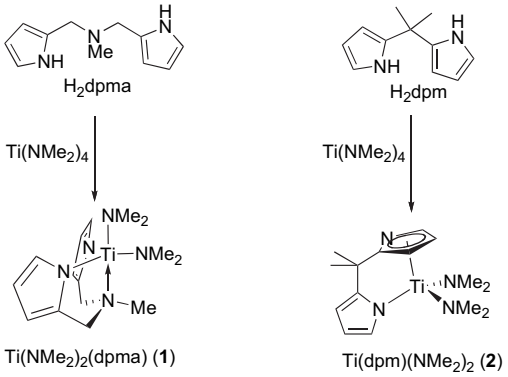
quantitative yield by reacting commercially available $Ti(NMe_2)_4$ with H_2dpma or H_2dpm (Scheme 2). The H_2dpma ligand is prepared[16] in a single step by Mannich condensation of pyrrole, formaldehyde, and methylamine hydrochloride in ethanol/water; whereas, H_2dpm is synthesized by condensation of pyrrole and acetone in the presence of trifluoroacetic acid (TFA).[17]



Scheme 1. Proposed catalytic cycle for iminoamination.



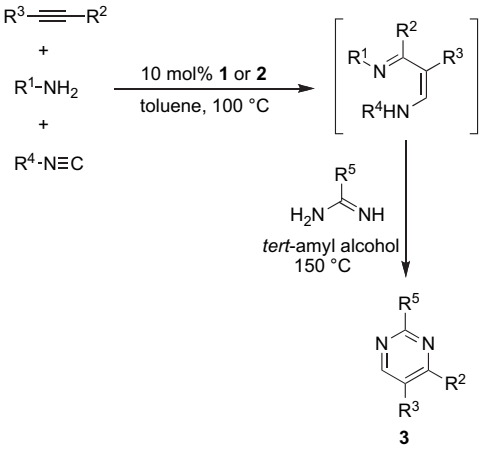
Scheme 2. Generation of titanium catalysts.

The multicomponent coupling reaction is quite effective for both terminal and internal alkynes with a variety of aliphatic and aromatic amines. Because the substituent on the isonitrile does not end up in the final pyrimidine product, *tert*-butylisonitrile was employed exclusively here due to its general applicability in this reaction. Ease of synthesis is an advantage of *t*-BuNC as well, which is readily prepared from *tert*-butylamine and chloroform in the presence of base.[18] Alternatively, the isonitrile is commercially available. Similarly in the case of the amine, we used inexpensive and readily available cyclohexylamine or aniline as these substituents are lost in the *cyclo*-condensation step of the one-pot synthesis.

Barluenga and co-workers have published many notable papers in '1-azabutadiene' chemistry where the intermediates were isolated from reactions of saturated nitriles with Schiff bases in the presence of $AlCl_3$.[19] Gupton and co-workers reported the synthesis of pyrimidines from vinylogous iminium salts, which were prepared in a few steps starting from α,β-unsaturated β-aminoketones.[20] These '1-azabutadienes' and vinylogous iminium salts are close derivatives of the iminoamination products used here; however, the available substitution patterns are quite different. In addition, the iminoamination procedure produces these useful intermediates in a one-step 3-component coupling procedure, and catalyst variations can be used in some cases to control regioselectivity giving different products from the same substrates (vide infra).

Initial studies focused on the condensation reaction of the isolated 3CC product with benzamidine hydrochloride. In these reactions, the pyrimidine compounds were isolated in 60–70% yield under optimized reaction conditions. With the optimal conditions in hand, the multicomponent coupling was carried out with phenylacetylene, cyclohexylamine, and *tert*-butylisonitrile followed by one-pot condensation with benzamidine hydrochloride. The resulting 2,5-diphenylpyrimidine was isolated in 51% yield in this one-pot methodology.

The general procedure involves the addition of amine (1 mmol), catalyst (10 mol %), alkyne (1 mmol), isonitrile (1–1.5 mmol), and 2 mL of toluene to a 40 mL pressure tube under nitrogen, which is sealed and heated at 100 °C with stirring. Once the multicomponent coupling reaction was complete as judged by GC–FID, the volatiles were removed in vacuo and 2 mL of *tert*-amyl alcohol along with amidine or amidine hydrochloride was added to the crude residue. After additional heating,[21] the product pyrimidine (**3**) was purified by chromatography or crystallization (Scheme 3).



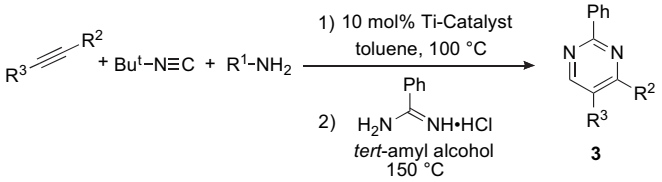
Scheme 3. One-pot synthesis of pyrimidines (**3**).

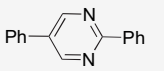
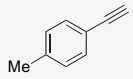
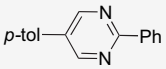
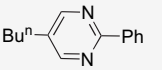
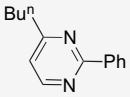
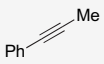
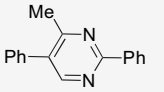
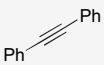
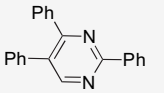
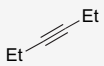
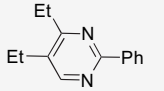
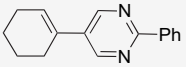
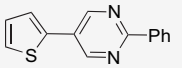
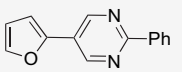
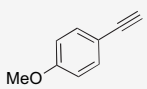
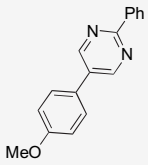
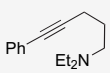
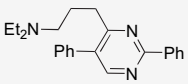
Some applications of this one-pot multicomponent coupling methodology are shown in Tables 1 and 2. Initial studies focused on the 3CC of a variety of different alkynes followed by *cyclo*-condensation with benzamidine hydrochloride to afford substituted pyrimidines. Most of the alkynes listed here formed only one 3CC product except in case of phenylacetylene (entry 3a), where ~5% of an isomer was observed. Moreover, heteroaromatic alkynes (entries 3i and 3j) as well as enynes (entry 3h) can be successfully converted to the corresponding pyrimidine compounds.

The regioselectivity of the multicomponent reaction is set by the [2+2]-cycloaddition reaction in conjunction with the relative trapping rates by isonitrile. The regioselectivity of the addition is electronically controlled when an arene is found on the alkyne triple bond through stabilization of a partial anionic charge adjacent to the metal in the azametallacyclobutene intermediate.[12b] This results in 5-(aryl)pyrimidine substitution being electronically favored for aryl substituted alkynes. For 1-hexyne, for example, it is possible to control the regioselectivity of the alkyne addition to get either 4- or 5-substitution with choice of catalyst (entries 3c and 3d).

For the second stage of the study, we chose to look at the multicomponent coupling product of phenylacetylene, *tert*-

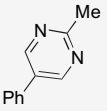
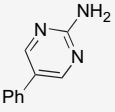
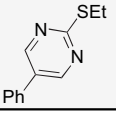
Table 1
Examples of pyrimidine (**3**) syntheses using benzamidine hydrochloride with different alkynes



	Alkyne	Catalyst	Product	Yield[a] % (GC)
a		**1**		51 (59)
b		**1**		40 (45)
c		**2**		43 (50)
d		**1**		51 (61)[b]
e		**1**		35 (43)[b]
f		**2**		17 (29)[b,c]
g		**2**		25 (36)[b]
h		**2**		31 (47)
i		**2**		27 (30)[b]
j		**2**		24[b]
k		**2**		31
l		**2**		38[b]

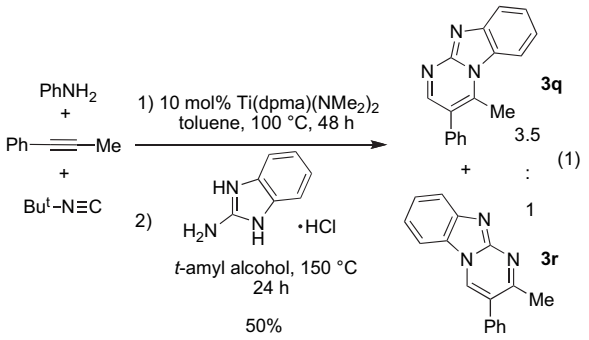
[a] Most reactions carried out with arylamine, alkyne, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst at 100 °C for 24–48 h. Once the 3CC is complete, product was heated at 150 °C in *tert*-amyl alcohol with amidines.
[b] Aniline was used in place of cyclohexylamine.
[c] Used 20 mol % Ti(dpm)$(NMe_2)_2$ at 125 °C.

Table 2
Examples of pyrimidine syntheses (**3**) using phenylacetylene and a variety of amidines

	Alkyne	Amidine	Catalyst	Product	Yield[a] %(GC)
m			**1**		43 (52)
n			**1a**		38 (44)
o			**1**		33
p			**1**		35 (45)

[a] Reactions carried out with arylamine, alkyne, and *tert*-butylisonitrile 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 *tert*-amyl alcohol with amidines.

butylisonitrile, and cyclohexylamine with a variety of different amidines (Table 2). All the amidines attempted reacted with similar efficiency in the second step of the reaction, and a large variety of 2-heteroatom substituted pyrimidines can likely be prepared in comparable yields.



In addition, the unsymmetrical 3CC product from 1-phenylpropyne, aniline, and *tert*-butylisonitrile was reacted with 2-aminobenzimidazole in a one-pot protocol. Two regioisomeric pyrimidine products (3q and 3r) were obtained in a 3.5:1 ratio (Eq. 1). The two isomers vary in the placement of the aromatic ring of the benzimidazole relative to the substituents on the pyrimidine ring. The structure of the major isomer was found by NOESY NMR experiments and apparently comes from initial attack of the 2-amino group on the less sterically encumbered site of the 1,3-diimine tautomer.

3. Conclusion

Titanium-catalyzed multicomponent coupling offers a ready route to 1,3-diimine tautomers, which can then be directly employed[22] in heterocyclic syntheses. This route to pyrimidines offers a simple, one-pot method to access pyrimidines with a variety of different substituents.

4. Experimental section

4.1. General considerations

All manipulations of air sensitive compounds were carried out in an MBraun dry box under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and removing water by running through activated alumina systems purchased from Solv-Tek. Deuterated solvents were dried over purple sodium benzophenone ketyl (C_6D_6) or phosphoric anhydride ($CDCl_3$) and distilled under a nitrogen atmosphere. Deuterated toluene was dried by passing through two columns of activated neutral alumina. ^1H and ^{13}C spectra were recorded on VXR-500 spectrometers. Alkynes were purchased either from Aldrich or from GFS chemicals and dried from CaO under dry nitrogen. Amines were purchased from Aldrich, dried over KOH, and distilled under dry nitrogen. 2-Ethynylthiophene[23] and 2-ethynylfuran[24] were made according to the literature procedures. Amidines were purchased either from Alfa Aesar or from TCI; however, 2-aminobenzimidazole was purchased from Aldrich. *tert*-Amyl alcohol was purchased from Eastman Chemical Co., was dried over Mg, and was distilled under dinitrogen.

4.2. General procedure for pyrimidine synthesis

In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar was loaded with amine (5 mmol), catalyst (10–20 mol %), alkyne (5 mmol), isonitrile (5–7.5 mmol), and 10 mL of dry toluene. The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated to the appropriate temperature for the desired time with vigorous stirring. After completion of the reaction as judged by GC–FID, the pressure tube was cooled to room temperature and volatiles were removed under reduced pressure. Then the same pressure tube was charged with amidine hydrochloride (7.5 mmol) in *tert*-amyl alcohol (10 mL) and heated to 150 °C for 24 h. After completion of the reaction, *tert*-amyl alcohol was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified either by column chromatography or by crystallization from a suitable solvent.

4.2.1. 2,5-Diphenylpyrimidine ***3a***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 4:1, which afforded the desired compound (588 mg, 51%) as a pale yellow solid. Mp: 179–180 °C (lit.[25] mp: 180–182). ^1H NMR ($CDCl_3$, 500 MHz): 7.43–7.46 (1H, m, Ar-H), 7.48–7.53 (5H, m, Ar-H), 7.61–7.63 (2H, m, Ar-H), 8.46–8.48 (2H, m, Ar-H), 9.01 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 126.8, 128.1, 128.6, 128.7, 129.4, 130.8, 131.7, 134.5, 137.2, 155.2, 163.4. MS (EI): *m*/*z* 232 (M^+). High resolution MS: *m*/*z* Calcd for $C_{16}H_{13}N_2^+$: 233.1079; found: 233.1075.

4.2.2. 2-Phenyl-5-(p-tolyl)pyrimidine ***3b***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), *p*-tolyl acetylene (580 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 4:1, which afforded the desired compound (500 mg, 40%) as a white solid. Mp: 150–151 °C. ^1H NMR ($CDCl_3$, 500 MHz): 2.42 (3H, s, CH_3), 7.32 (2H, d, *J*=8 Hz, Ar-H), 7.49–7.52 (5H, m, Ar-H), 8.47–8.49 (2H, m, Ar-H), 9.01 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 21.2, 126.6, 128.1, 128.7, 130.1, 130.9, 131.3, 131.7, 136.8, 139.0, 154.9, 162.7. MS (EI): *m*/*z* 246 (M^+). High resolution MS: *m*/*z* Calcd for $C_{17}H_{15}N_2^+$: 247.1235; found: 247.1236.

4.2.3. 5-Butyl-2-phenylpyrimidine ***3c***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), 1-hexyne (575 μL, 5 mmol), and $Ti(NMe_2)_2$(dpm) (154 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 140 °C for 36 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 4:1, which afforded the desired compound (457 mg, 43%) as a yellow-red liquid. ^1H NMR ($CDCl_3$, 500 MHz): 0.95 (3H, t, *J*=7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.37–1.42 (2H, m, $CH_2CH_2CH_2CH_3$), 1.61–1.68 (2H, m, $CH_2CH_2CH_2CH_3$), 2.66 (2H, t, *J*=7.5 Hz, $CH_2CH_2CH_2CH_3$), 7.49–7.50 (3H, m, Ar-H), 8.45–8.47 (2H, m, Ar-H), 8.70 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 13.7, 22.1, 29.9, 32.8, 127.8, 128.5, 130.3, 132.9, 137.6, 157.0, 162.6. MS (EI): *m*/*z* 212 (M^+). High resolution MS: *m*/*z* Calcd for $C_{14}H_{17}N_2^+$: 213.1392; found: 213.1395.

4.2.4. 4-Butyl-2-phenylpyrimidine ***3d***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (570 μL, 5 mmol), aniline (460 μL, 5 mmol), 1-hexyne (575 μL, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 140 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 3:1, which afforded the desired compound (540 mg, 51%) as a yellow-red liquid (~10% of the other isomer was also formed in the reaction). ^1H NMR ($CDCl_3$, 500 MHz): 0.95 (3H, t, *J*=7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.37–1.43 (2H, m, $CH_2CH_2CH_2CH_3$), 1.74–1.80 (2H, m, $CH_2CH_2CH_2CH_3$), 2.80 (2H, t, *J*=7.5 Hz, $CH_2CH_2CH_2CH_3$), 7.01 (1H, d, *J*=5 Hz, 5-CH pyrimidine), 7.45–7.47 (3H, m, Ar-H), 8.42–8.44 (2H, m, Ar-H), 8.64 (1H, d, *J*=5 Hz, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 13.9, 22.4, 30.7, 37.7, 117.9, 128.4, 128.5, 130.4, 137.9, 156.8, 164.3, 171.0. MS (EI): *m*/*z* 212 (M^+). High resolution MS: *m*/*z* Calcd for $C_{14}H_{17}N_2^+$: 213.1392; found: 213.1388.

4.2.5. 4-Methyl-2,5-diphenylpyrimidine ***3e***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (680 μL, 5.5 mmol), aniline (460 μL, 5 mmol), 1-phenylpropyne (625 μL, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 48 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 4:1, which afforded the desired compound (428 mg, 35%) as a white solid. Mp: 83–84 °C. ^1H NMR ($CDCl_3$, 500 MHz): 2.57 (3H, s, CH_3), 7.35–7.37 (2H, m, Ar-H), 7.40–7.44 (1H, m, Ar-H), 7.46–7.51 (5H, m, Ar-H), 8.46–8.48 (2H, m, Ar-H), 8.59 (1H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 23.1, 128.1, 128.5, 128.7, 129.0, 130.5, 132.3, 136.1, 137.5, 156.6, 162.9, 164.6. MS (EI): *m*/*z* 246 (M^+). High resolution MS: *m*/*z* Calcd for $C_{17}H_{15}N_2^+$: 247.1235; found: 247.1238.

4.2.6. 2,4,5-Triphenylpyrimidine ***3f***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile

(513 μL, 4.5 mmol), aniline (276 μL, 3 mmol), diphenylacetylene (534 mg, 3 mmol), and $Ti(NMe_2)_2(dpm)$ (186 mg, 0.6 mmol) in toluene (6 mL) and was heated for 48 h at 125 °C. Volatiles were removed and benzamidine hydrochloride (0.702 g, 4.5 mmol) in dry *tert*-amyl alcohol (6 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (156 mg, 17%) as a yellow-orange solid. Mp: 108–110 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.26–7.28 (2H, m, Ar-H), 7.30–7.33 (2H, m, Ar-H), 7.36–7.39 (4H, m, Ar-H), 7.51–7.54 (3H, m, Ar-H), 7.57–7.58 (2H, m, Ar-H), 8.58–8.60 (2H, m, Ar-H), 8.81 (1H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 127.9, 128.0, 128.2, 128.5, 128.7, 129.3, 130.0, 130.6, 130.8, 136.6, 137.5, 137.9, 158.6, 163.2, 163.3. MS (EI): *m*/*z* 308 (M^+). High resolution MS: *m*/*z* Calcd for $C_{22}H_{17}N_2^+$: 309.1392; found: 309.1399.

4.2.7. 4,5-Diethyl-2-phenylpyrimidine ***3g***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), aniline (460 μL, 5 mmol), 3-hexyne (410 mg, 5 mmol), and $Ti(NMe_2)_2(dpm)$ (154 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 110 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 140 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 3:1, which afforded the desired compound (265 mg, 25%) as a red liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.29 (3H, t, *J*=7.5 Hz, 5-CH_2CH_3), 1.41 (3H, t, *J*=7.5 Hz, 4-CH_2CH_3), 2.69 (2H, q, *J*=7.5 Hz, 5-CH_2CH_3), 2.88 (2H, q, *J*=7.5 Hz, 4-CH_2CH_3) 7.46–7.50 (3H, m, Ar-H), 8.46–8.48 (2H, m, Ar-H), 8.51 (1H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 12.2, 14.4, 22.4, 27.3, 127.8, 128.4, 130.0, 131.6, 138.1, 156.1, 162.1, 169.1. MS (EI): *m*/*z* 212 (M^+). High resolution MS: *m*/*z* Calcd for $C_{14}H_{17}N_2^+$: 213.1392; found: 213.1396.

4.2.8. 5-Cyclohexenyl-2-phenylpyrimidine ***3h***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), cyclohexenylacetylene (530 mg, 5 mmol), and $Ti(NMe_2)_2(dpm)$ (154 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (1.17 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was hexanes/ethyl acetate 4:1, which afforded the desired compound (352 mg, 31%) as a pale yellow solid. Mp: 97–98 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.66–1.70 (2H, m, CH_2), 1.78–1.83 (2H, m, CH_2), 2.23–2.25 (2H, m, CH_2), 2.40–2.41 (2H, m, CH_2), 6.25–6.26 (1H, m, CH), 7.45–7.47 (3H, m, Ar-H), 8.41 (2H, d, *J*=8 Hz, Ar-H), 8.77 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 21.7, 22.5, 25.9, 26.5, 127.8, 127.9, 128.6, 130.4, 131.1, 132.6, 137.4, 153.4, 162.6. MS (EI): *m*/*z* 236 (M^+). High resolution MS: *m*/*z* Calcd for $C_{16}H_{17}N_2^+$: 237.1392; found: 237.1384.

4.2.9. 2-Phenyl-5-(thiophen-2-yl)pyrimidine ***3i***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (374 mg, 4.5 mmol), aniline (279 mg, 3 mmol), 2-ethynylthiophene (324 mg, 3 mmol), and $Ti(NMe_2)_2(dpm)$ (93 mg, 0.3 mmol) in toluene (6 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (0.515 g, 3.3 mmol) in dry *tert*-amyl alcohol (6 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (185 mg, 27%) as a yellow solid. Mp: 118–119 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.16 (1H, dd, *J*=9 and 5 Hz, Ar-H), 7.42–7.43 (2H, m, Ar-H), 7.47–7.50 (3H, m, Ar-H), 8.44–8.46 (2H, m, Ar-H), 9.00 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 124.8, 126.1, 126.8, 128.0, 128.5, 128.6, 130.8, 136.8, 137.0, 153.7, 163.1. MS (EI): *m*/*z* 238 (M^+). High resolution MS: *m*/*z* Calcd for $C_{14}H_{11}N_2S^+$: 239.0643; found: 239.0642.

4.2.10. 5-(Furan-2-yl)-2-phenylpyrimidine ***3j***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (375 mg, 4.5 mmol), aniline (279 mg, 3 mmol), 2-ethynylfuran (276 mg, 3 mmol), and $Ti(NMe_2)_2(dpm)$ (93 mg, 0.3 mmol) in toluene (6 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (0.515 g, 3.3 mmol) in dry pyridine (6 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (160 mg, 24%) as a yellow solid. Mp: 151–152 °C (lit.[26] mp: 153–154). ^{1}H NMR ($CDCl_3$, 500 MHz): 6.56 (1H, dd, *J*=3.5 and 1.5 Hz, Ar-H), 6.87 (1H, d, *J*=3.5 Hz, Ar-H), 7.50–7.52 (3H, m, Ar-H), 7.59 (1H, d, *J*=1.5 Hz, Ar-H), 8.49–8.51 (2H, m, Ar-H), 9.11 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 107.3, 112.0, 122.6, 128.1, 128.6, 130.7, 137.2, 143.7, 148.6, 152.1, 162.8. MS (EI): *m*/*z* 222 (M^+). High resolution MS: *m*/*z* Calcd for $C_{14}H_{11}N_2O^+$: 223.0865; found: 223.0871.

4.2.11. 5-(4-Methoxyphenyl)-2-phenylpyrimidine ***3k***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (513 μL, 4.5 mmol), cyclohexylamine (297 mg, 3 mmol), *p*-methoxyphenylacetylene (396 mg, 3 mmol), and $Ti(NMe_2)_2(dpm)$ (93 mg, 0.3 mmol) in toluene (6 mL) and was heated for 24 h at 100 °C. Volatiles were removed and benzamidine hydrochloride (0.702 g, 4.5 mmol) in dry *tert*-amyl alcohol (6 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 85:15, which afforded the desired compound (245 mg, 31%) as a white solid. Mp: 170–172 °C (lit.[27] mp: 174–175). ^{1}H NMR ($CDCl_3$, 500 MHz): 3.86 (3H, s, OCH_3), 7.03–7.04 (2H, m, Ar-H), 7.48–7.50 (3H, m, Ar-H), 7.54–7.56 (2H, m, Ar-H), 8.45–8.47 (2H, m, Ar-H), 8.97 (2H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 55.4, 114.9, 126.8, 127.9, 128.0, 128.6, 130.6, 131.3, 137.3, 154.7, 160.3, 162.8. MS (EI): *m*/*z* 262 (M^+). High resolution MS: *m*/*z* Calcd for $C_{17}H_{15}ON_2^+$: 263.1184; found: 263.1183.

4.2.12. 3-(2,5-Diphenylpyrimidin-4-yl)-N,N-diethylpropan-1-amine ***3l***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (85 μL, 0.75 mmol), aniline (46 μL, 0.5 mmol), *N*,*N*-diethyl-5-phenylpent-4-yn-1-amine (107.5 mg, 0.5 mmol), and $Ti(NMe_2)_2(dpm)$ (15.4 mg, 0.05 mmol) in toluene (1 mL) and was heated for 36 h at 125 °C. Volatiles were removed and benzamidine hydrochloride (118 mg, 0.75 mmol) in dry *tert*-amyl alcohol (1 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate/triethylamine 78:20:2, which afforded the desired compound (66 mg, 38%) as a red oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.93 (6H, t, *J*=7 Hz, CH_2CH_3), 1.91–1.97 (2H, m, $CH_2CH_2CH_2NEt_2$), 2.41–2.47 (6H, m, $CH_2CH_2CH_2NEt_2$ and CH_2CH_3), 2.81 (2H, t, *J*=8 Hz, $CH_2CH_2CH_2NEt_2$), 7.34–7.50 (8H, m, Ar-*H*), 8.49–8.51 (2H, m, Ar-H), 8.56 (1H, s, 4-CH pyrimidine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 11.7, 25.6, 32.9, 46.7, 52.4, 128.0, 128.1, 128.4, 128.6, 129.1, 130.4, 132.2, 136.2, 137.7, 156.8, 162.9, 167.6. MS (EI): *m*/*z* 345 (M^+). High resolution MS: *m*/*z* Calcd for $C_{23}H_{28}N_3^+$: 346.2283; found: 346.2278.

4.2.13. 5-Phenylpyrimidine ***3m***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2(dpma)$ (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were

removed and formamidine acetate (0.780 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 140 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was initially hexanes/ethyl acetate 7:3 and increased to 1:19 methanol/ethylacetate, which afforded the desired compound in 43% (337 mg) yield (5% of the other isomer could not be separated). Major isomer ^{1}H NMR ($CDCl_3$, 500 MHz): 7.42–7.46 (1H, m, Ar-H), 7.47–7.51 (2H, m, Ar-H), 7.54–7.56 (2H, m, Ar-H), 8.92 (1H, s, 4-CH pyrimidine), 9.18 (1H, s, 2-CH pyrimidine). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 126.9, 129.0, 129.4, 134.2, 134.3, 154.9, 157.5. MS (EI): *m*/*z* 156 (M^+). High resolution MS: *m*/*z* Calcd for $C_{10}H_9N_2^+$: 157.0666; found: 157.0666.

4.2.14. 2-Methyl-5-phenylpyrimidine ***3n***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and acetamidine hydrochloride (0.709 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 140 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 4:1, which afforded the desired compound (321 mg, 38%) as a pale yellow solid. Mp: 57–58 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.79 (3H, s, CH_3), 7.41–7.45 (1H, m, Ar-H), 7.47–7.51 (2H, m, Ar-H), 7.53–7.55 (2H, m, Ar-H), 8.85 (2H, s, 4-CH pyrimidine). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 25.4, 126.8, 128.7, 129.3, 131.2, 134.2, 154.9, 166.5. MS(EI): *m*/*z* 170 (M^+). High resolution MS: *m*/*z* Calcd for $C_{11}H_{11}N_2^+$: 171.0922; found: 171.0918.

4.2.15. 5-Phenylpyrimidin-2-amine ***3o***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and guanidine hydrochloride (0.528 g, 7.5 mmol) in dry pyridine (10 mL) was added. The mixture was heated to 140 °C for 24 h. The crude product was purified by recrystalization from ethanol, which afforded the desired compound (282 mg, 33%) as a pale brown solid. Mp: 158–159 °C (lit.[28] mp: 161–163). ^{1}H NMR ($CDCl_3$, 500 MHz): 5.23 (2H, br s, NH_2), 7.33–7.36 (1H, m, Ar-H), 7.41–7.47 (4H, m, Ar-H), 8.52 (2H, s, 4-CH pyrimidine). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 125.0, 126.0, 127.6, 129.2, 135.1, 156.4, 161.9. MS (EI): *m*/*z* 171 (M^+). High resolution MS: *m*/*z* Calcd for $C_{10}H_{10}N_3^+$: 172.0875; found: 172.0873.

4.2.16. 2-(Ethylthio)-5-phenylpyrimidine ***3p***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (855 μL, 7.5 mmol), cyclohexylamine (495 mg, 5 mmol), phenylacetylene (510 mg, 5 mmol), and $Ti(NMe_2)_2$(dpma) (162 mg, 0.5 mmol) in toluene (10 mL) and was heated for 24 h at 100 °C. Volatiles were removed and *S*-ethylisothiourea hydrobromide (1.39 g, 7.5 mmol) in dry *tert*-amyl alcohol (10 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 85:15, which afforded the desired compound (350 mg, 35%) as white solid. Mp: 70–71 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.41 (3H, t, *J*=7 Hz, CH_2CH_3), 3.19 (2H, q, *J*=7.5 Hz, CH_2CH_3), 7.38–7.42 (1H, m, Ar-H), 7.45–7.48 (2H, m, Ar-H), 7.50–7.52 (2H, m, Ar-H), 8.71 (2H, s, 4-CH pyrimidine). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 14.4, 25.3, 126.5, 128.4, 129.3, 134.4, 155.2, 171.1. MS (EI): *m*/*z* 216 (M^+). High resolution MS: *m*/*z* Calcd for $C_{12}H_{13}SN_2^+$: 217.0799; found: 217.0802.

4.2.17. 4-Methyl-3-phenylpyrimido[1,2-a]-benzimidazole ***3q***. The general procedure was followed. The reaction was carried out with *tert*-butylisonitrile (136 μL, 1.2 mmol), aniline (92 μL, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and $Ti(NMe_2)_2$(dpma) (32.3 mg, 0.1 mmol) in toluene (2 mL) and was heated for 48 h at 100 °C. Volatiles were removed and 2-aminobenzimidazole (200 mg, 1.5 mmol) in dry *tert*-amyl alcohol (3 mL) was added. The mixture was heated to 145–150 °C for 24 h. Purification was accomplished by column chromatography on silica. The eluent was Et_3N/ethyl acetate 3:97, which afforded the desired compound (131 mg, 50%) as a mixture of two isomers in 3.5:1 ratio (the ratio of the two isomers was confirmed from the crude product mixture before purification). Major isomer, ^{1}H NMR ($CDCl_3$, 500 MHz): 3.01 (3H, s, CH_3), 7.38–7.39 (3H, m, Ar-H), 7.46–7.48 (1H, m, Ar-H), 7.50–7.53 (2H, m, Ar-H), 7.56–7.59 (1H, m, Ar-H), 8.05 (1H, d, *J*=8.5 Hz, Ar-H), 8.10 (1H, d, *J*=8.5 Hz, Ar-H), 8.70 (1H, s, 4-CH pyrimidine). The ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) for the mixture of isomers: 18.4, 25.9, 110.4, 115.2, 120.4, 120.6, 121.4, 121.7, 126.0, 126.3, 128.4, 128.6, 128.9, 129.0, 129.6, 130.1, 130.9, 134.7, 145.0, 145.4, 150.9, 156.5. The ^{1}H, ^{13}C, and 2D spectra are supplied in the NMR file of the Supplementary data. MS (EI): *m*/*z* 259 (M^+). High resolution MS: *m*/*z* Calcd for $C_{17}H_{14}N_3^+$: 260.1188; found: 260.1186.

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Supplementary data

^{1}H and ^{13}C NMR spectra for all the pyrimidine products can be found in the online version at doi:10.1016/j.tet.2010.02.066.

References and notes

1. Lagoja, I. M. *Chem. Biodivers.* **2005**, *2*, 1.
2. Ahluwalia, V. K.; Kaila, N.; Bala, S. *Indian J. Chem., Sect. B* **1987**, *26B*, 700.
3. El-Hashash, M. A.; Mahmoud, M. R.; Madboli, S. A. *Indian J. Chem., Sect. B* **1993**, *32B*, 449.
4. Keutzberger, A.; Gillessen, J. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 370.
5. Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T. *N. Engl. J. Med.* **1987**, *317*, 185.
6. Joffe, A. M.; Farley, J. D.; Linden, D.; Goldsand, G. *Am. J. Med.* **1989**, *87*, 332.
7. For a review on related enaminones in synthesis see Elassar, A. Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.
8. For reviews see: (a) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667; (b) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489.
9. (a) Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880; (b) Banerjee, S.; Shi, Y.; Cao, C.; Odom, A.L. J. Organometallic Chem., 690, 5066. 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.
10. (a) For a review on azadienes in synthesis see Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379 See also; (b) Calvo, L. A.; Gonzalez-Nogal, A. M.; Gonzalez-Ortega, A.; Sañudo, M. C. *Tetrahedron Lett.* **2001**, *42*, 8981 for related silyl isoxazole chemistry.
11. For a recent review on hydroamination see Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.
12. (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708; (b) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753; (c) McGrane, P. L.; Jenson, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459; (d) Zi, G.; Blosch, L. L.; Jia, L.; Andersen, R. A. *Organometallics* **2005**, *24*, 4602; (e) Poise, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 13405; (f) Duncan, A. P.; Bergman, R. G. *Chem. Rec.* **2002**, *2*, 431; (g) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407.
13. Vujkovic, N.; Fillol, J. L.; Ward, B. D.; Wadepohl, H.; Mountford, P.; Gade, L. H. *Organometallics* **2008**, *27*, 2518 For a recently characterized example of the proposed 5-membered metallacyclic intermediate prepared by isonitrile insertion see.
14. Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2001**, *40*, 1987.
15. (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.
16. Li, Y.; Turnas, A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2002**, *41*, 6298.
17. 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.
18. Gokel, G. W.; Widera, R. P.; Weber, W. P. *Org. Synth.* **1976**, *55*, 96.

19. (a) For reviews on the extensive work of Barluenga and coworkers on applications of 1,3-diimines to organic synthesis see Barluenga, J.; Tomás, M. *Adv. Heterocycl. Chem.* **1993**, *57*, 1; (b) For some references related more specifically to 1,3-diimines reactions related to those here see Barluenga, J. *Bull. Soc. Chim. Belg.* **1988**, *97*, 545; (c) Barluenga, J.; Rubio, E.; Rubio, V.; Muniz, L.; Iglesias, M. J.; Gotor, V. *J. Chem. Res., Synop.* **1985**, 124; (d) Barluenga, J.; Iglesias, M. J.; Gotor, V. *Synthesis* **1987**, 662; (e) Gotor, V.; Brieva, R.; Aguirre, A.; Garcia-Granda, S.; Gomez-Beltran, F. *Heterocycles* **1989**, *29*, 1695; (f) Barluenga, J.; López-Ortiz, J. F.; Tomás, M.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1891; (g) Barluenga, J.; Jardón, J.; Rubio, V.; Gotor, V. *J. Org. Chem.* **1983**, *48*, 1379.
20. Gupton, J. T.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Vargas, M.; Hosein, K. N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689.
21. None of the reaction times have been fully optimized. Reactions were generally run for about 24 h.
22. (a) Majumder, S.; Gipson, K. R.; Staples, R. J.; Odom, A. L. *Adv. Synth. Catal.* **2009**, *351*, 2013; (b) Majumder, S.; Gipson, K. R.; Odom, A. L. *Org. Lett.* **2009**, *11*, 4720.
23. Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, *17*, 4044.
24. Carpita, A.; Rossi, R.; Veracini, C. A. *Tetrahedron* **1985**, *41*, 1919.
25. Ibrahim, Y. B.; Al-Awadi, N. A.; Ibrahim, M. R. *Tetrahedron* **2004**, *60*, 9121.
26. Promel, R.; Cardon, A.; Daniel, M.; Jacques, G.; Vandersmissen, A. *Tetrahedron Lett.* **1968**, *26*, 3067.
27. Mosquera, A.; Riveiros, R.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **2008**, *10*, 3745.
28. Protopopova, T. V.; Klimko, V. T.; Skoldinov, A. P. *Khimicheskaya Nauka i Promyshlennost* **1959**, *4*, 805.