Three-Component Coupling Sequence for the Regiospecific Synthesis of Substituted Pyridines

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S *Supporting Information*

ABSTRACT: A de novo synthesis of substituted pyridines is described that proceeds through nucleophilic addition of a dithiane anion to an α,β-unsaturated carbonyl followed by metallacycle-mediated union of the resulting allylic alcohol with preformed trimethylsilane-imines (generated in situ by the low-temperature reaction of lithium hexamethyldisilazide with an aldehyde) and Ag(I)- or Hg(II)-mediated ring closure. The process is useful for the convergent assembly of di- through penta-substituted pyridines with complete regiochemical control.

--- = bonds forged in this convergent pyridine synthesis.
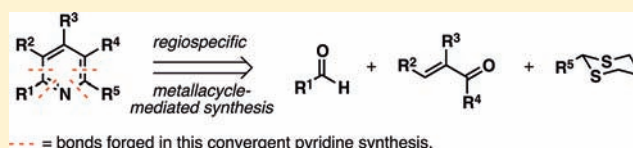
1. INTRODUCTION

Aromatic nitrogen heterocycles play prominent roles in natural products and pharmaceutical agents. Of these, substituted pyridines are particularly abundant.[1] As a result, pyridine synthesis has attracted the attention of members of the scientific community for more than 140 years. While many chemical methods exist for the preparation of these heteroaromatics, the search for new strategies that offer concise and regiospecific access remain a topic of considerable interest.[1]

With our sights set on the development of a highly convergent pyridine synthesis that proceeds from readily available starting materials, we have focused on realization of the retrosynthetic strategy depicted in Figure 1. Here, four central bonds of the pyridine are targeted for synthesis via stepwise union of an aldehyde **2**, an α,β-unsaturated carbonyl system **3**, and a dithiane **4** through a process that delivers pyridine products as single regioisomers.

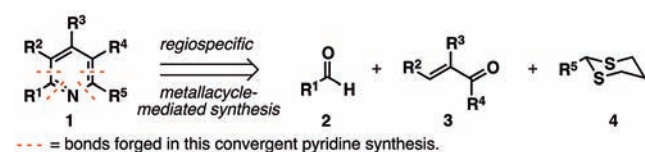--- = bonds forged in this convergent pyridine synthesis.

Figure 1. A new approach to pyridine synthesis by metallacycle-mediated C−C bond formation.

This proposed strategy marks a substantial departure from traditional approaches based on carbonyl condensation chemistry (i.e. Hantzch-like dihydropyridine synthesis)[2] and offers great flexibility in the nature and substitution of the pyridine products that can be accessed. Aside from the present study, a great many modern advances have been described that provide access to substituted pyridines by synthesis strategies that embrace a variety of diverse modes of chemical reactivity and key bond-forming reactions that are distinct from those

under pursuit. As illustrated in Figure 2, these include Ru-catalyzed cycloisomerization,[3] Cu-catalyzed cross-coupling of vinylboronic acids and oxime O-carboxylates,[4] Rh-catalyzed C−H activation/alkyne insertion,[5] Rh-carbenoid-catalyzed ring expansion of isoxazoles,[6] electrophilic activation of vinyl-/aryl-amides and subsequent coupling with π-nucleophiles,[7] cycloaddition,[8] and ring-closing metathesis[9] (not depicted).

Distinct from these are Reppe-inspired syntheses of pyridines that proceed by metallacycle-mediated union of alkynes with a nitrile via [2 + 2 + 2] chemistry (Figure 2,vii).[10] While elegant and highly convergent, these metallacycle-mediated processes remain substantially limited in scope, suffering from the great challenges associated with controlling regioselectivity in metallacycle-mediated [2 + 2 + 2] annulation.[11]

In a strategically distinct approach to metallacycle-mediated pyridine synthesis that does not proceed by [2 + 2 + 2] annulation, we aimed to accomplish a simple, modular, and regiospecific three-component coupling sequence. As illustrated in Figure 3, substituted pyrdines (**1**) were envisioned to derive from Hg(II)- or Ag(I)-mediated cyclization of a suitably functionalized primary homoallylic amine **A**, itself derived from the metallacycle-mediated union of an aldehyde **2** with lithium hexamethyldisilazide (LiHMDS) and a dithiane-containing allylic alcohol **5**.[12] This latter coupling partner was thought to be readily available from selective 1,2-addition of a dithiane anion (**4**) to an α,β-unsaturated carbonyl system (**3**).

While built on our recently described three-component coupling reaction for the synthesis of primary homoallylic amines from the union of aldehydes with LiHMDS and an allylic alcohol,[12] the current pursuit was aimed at accomplishing a significantly more demanding process. The increased challenges associated with this pursuit span considerations regarding both reactivity and stereoselectivity. First, chemical
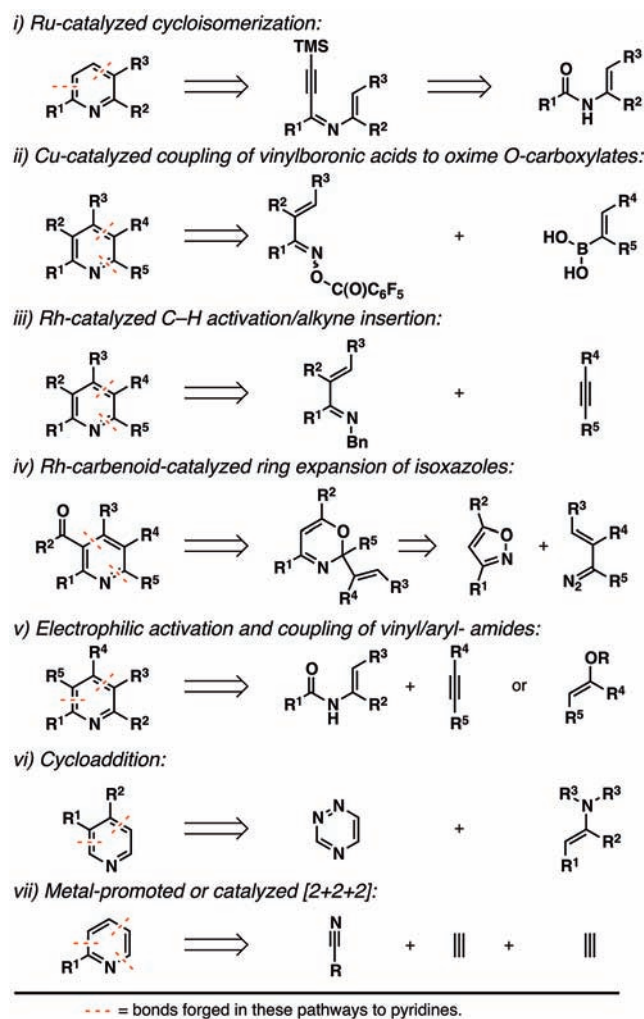
Figure 2. Some modern strategies for de novo pyridine synthesis.
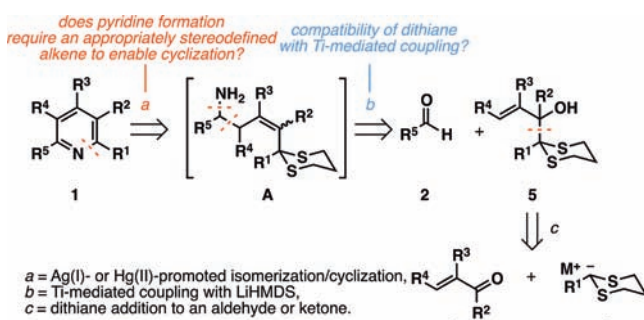

Figure 3. Concerns regarding reactivity and selectivity.

compatibility of the dithiane group of **5** with the reaction conditions for Ti-mediated coupling was thought to define a potential barrier to success. It is well established that low-valent Ti reagents (specifically, Cp$_2$Ti−) are capable of converting dithianes to the corresponding metal−carbene, and elegant examples of this process have been employed in synthesis campaigns.[13] Second, our established Ti-mediated allylic alcohol−imine coupling process is not uniformly (Z)-selective. If (Z)-selectivity in the union of **2** and **5** is necessary to enable subsequent ring closure/oxidation to the pyridine, then only a small subset of substituted allylic alcohols would be of utility in this process (R^3 ≠ H; R^2 = H).[14] As such, the general strategy
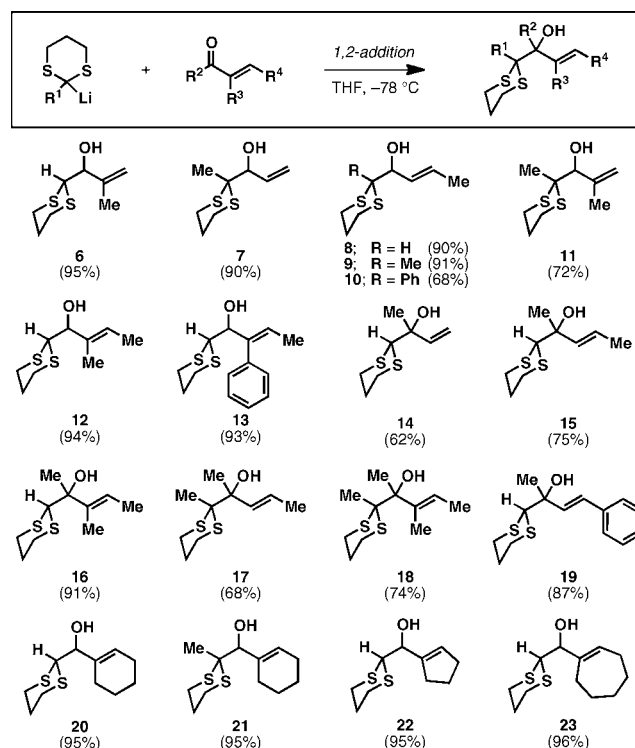
Figure 4. Step 1: 1,2-addition of dithiane anions to α,β-unsaturated aldehydes and ketones. Reaction conditions: n-BuLi, dithiane, THF (−20 °C), then −78 °C, and add aldehyde or ketone (see also Supporting Information).
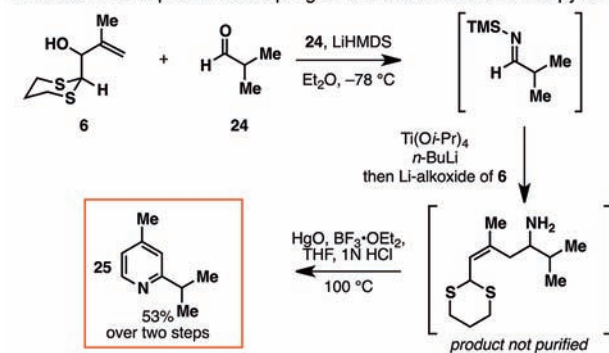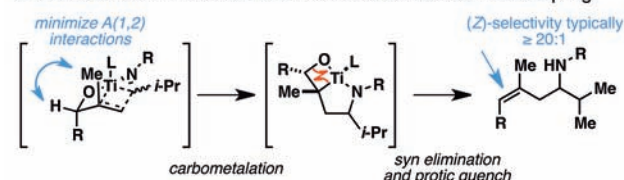

Figure 5. Initial success in Ti-mediated coupling and Hg-mediated cyclization.

depicted in Figure 3 had the potential of being rather limited in its ability to access a range of substituted pyridines. That said, if conditions for cyclization could be found to enable rapid and reversible alkene isomerization prior to ring closure, the strategy depicted in Figure 3 would be of extremely broad utility as a means to access a great variety of differentially substituted pyridines.

Following, is a description of our studies focused on the realization of this approach to de novo pyridine synthesis that documents the compatibility of a dithiane with the targeted Ti-mediated bond construction (**5** + **2** → **A**; Figure 3) and the ability to advance (*E*)- or (*Z*)-alkene-containing homoallylic amines to a wide range of subsisisted pyridine products (**A** → **1**).

2. RESULTS

The first step of this three-component coupling strategy to de novo pyridines based on selective 1,2-addition of a dithiane anion to an α,β-unsaturated ketone or aldehyde typically proceeds with very high levels of efficiency. As depicted in Figure 4, a range of substituted allylic alcohols can be prepared by this process, including those that contain secondary and tertiary alcohols as well as mono-, di-, and trisubstituted alkenes (**6**–**23**).
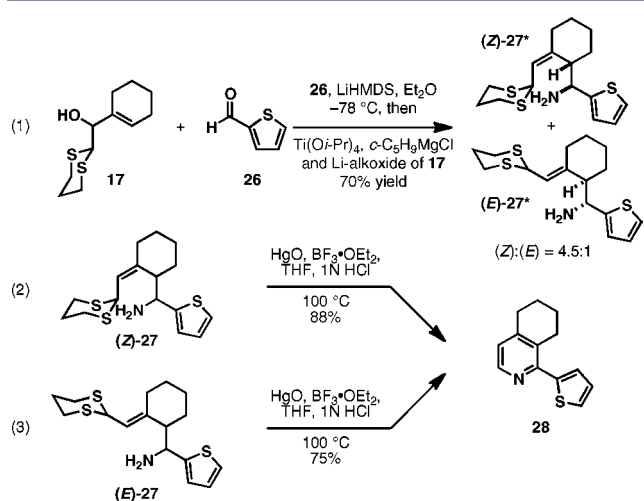

Figure 6. Alkene geometry is not relevant in the pyridine forming sequence. * = relative sp^3 stereochemistry of products (*Z*)- and (*E*)-**27** was not determined. Relative stereochemistry depicted for these isomers was assigned from our empirical model.[14]

With sights now set on the metallacycle-mediated coupling step of the planned pyridine synthesis, we examined the reactivity of allylic alcohol **6** in Ti-mediated reductive cross-coupling with aldehyde **24** (Figure 5A). Here, we were delighted to find that convergent coupling proceeded effectively, despite the presence of the dithiane, and the primary homoallylic amine product was advanced to the 2,4-disubstituted pyridine **25** in 53% yield (over the two-step sequence) as a single substitutional isomer. While we did not isolate the proposed homoallylic amine intermediate in this sequence, previous experiences[14] with Ti-mediated reductive cross-coupling reactions of related allylic alcohol (i.e., those containing 1,1-disubstituted alkenes) led to the expectation that this coupling reaction proceeds with very high levels of (*Z*)-selectivity (Figure 5B).

Moving on, we explored the role of alkene geometry in the Hg(II)-promoted ketal removal/cyclization and subsequent aromatization process. As depicted in eq 1 of Figure 6, reductive cross-coupling of the cyclohexenyl-containing allylic alcohol **17** with the heteroaromatic aldehyde **26** proceeds with modest stereoselection to deliver a mixture of two isomeric products **27** (*Z*:*E* = 4.5:1). Upon separation of this product mixture, each isomer was successfully converted to the hydroisoquinoline **28** with similar efficiencies (75 and 88% yields; eqs 2 and 3).

This finding, that alkene geometry does not play an important role in the pyridine-forming process, has profound impact on the potential utility of this general strategy to pyridine synthesis. Being unbound by a specific allylic alcohol substitution pattern as a means to render the reductive cross-coupling (*Z*)-selective, this approach to pyridine synthesis can embrace the participation of a host of substrates that contain widely varying substitution about the central allylic alcohol motif. As a result, this pyridine synthesis provides regiospecific access to a great variety of differentially substituted systems. As illustrated in Figure 7, coupling reactions employing benzaldehyde result in the generation of a range of 2-Ph-substituted pyridines that span disubstituted [2,4- (**29**), 2,5- (**30**), 2,6- (**31**), 2,3- (**32**)], trisubstituted [2,3,5- (**33**), 2,3,4- (**34**),
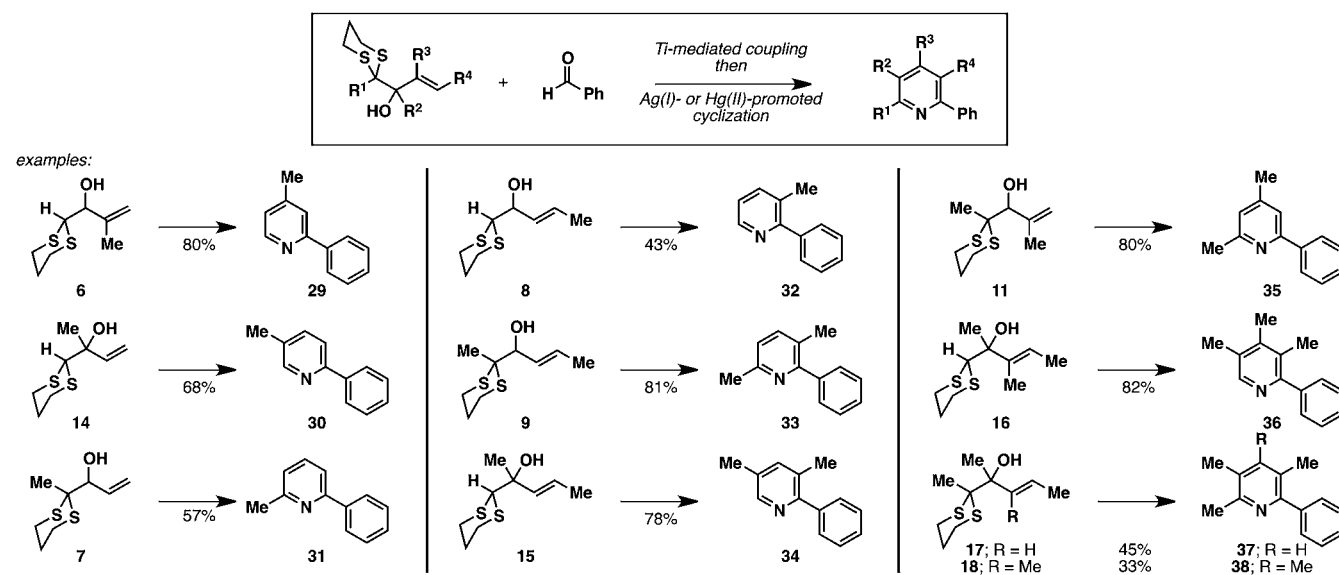

Figure 7. Regiospecific entry to a range of 2-Ph-substituted pyridines. Reaction conditions: (1) Ti-mediated coupling: aldehyde (2 equiv), LiHMDS, Et$_2$O, then Ti(Oi-Pr)$_4$, c-C$_5$H$_9$MgCl or n-BuLi, then add Li-alkoxide of allylic alcohol (1 equiv); (2) cyclization: HgO, BF$_3$·OEt$_2$, HCl, and THF (100 °C).
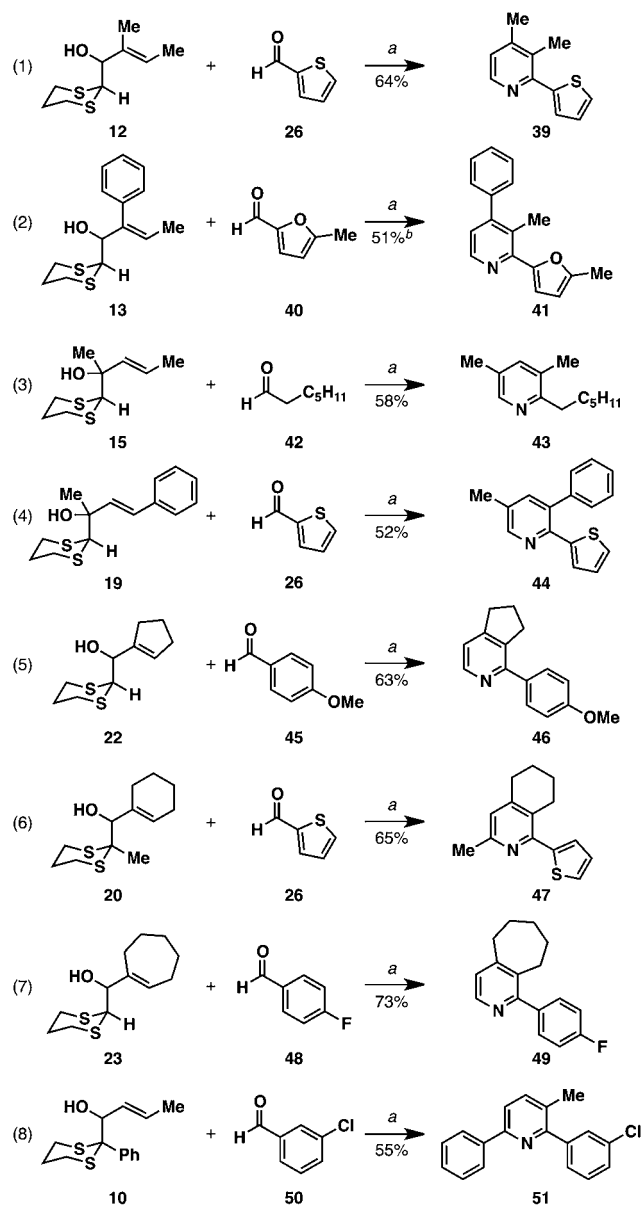
Figure 8. Exploring the scope of this metallacycle-mediated approach to de novo pyridine synthesis. Reaction conditions: (a) Ti-mediated coupling: aldehyde (2 equiv), LiHMDS, Et₂O, then Ti(Oi-Pr)₄, c-C₅H₉MgCl or n-BuLi, then add Li-alkoxide of allylic alcohol (1 equiv); cyclization: HgO, BF₃·OEt₂, HCl, and THF (100 °C); (b) AgNO₃ was employed for the cyclization step: AgNO₃, THF, and H₂O (60 °C).

2,4,6- [**35**]], tetrasubstituted [2,3,4,5- (**36**), 2,3,5,6- (**37**)], and even pentasubstituted (**38**) products.

With a firm foundation of results supporting the great flexibility of this pyridine synthesis for the preparation of 2-Ph-substituted pyridines, effort was focused on exploring the suitability of this process for preparing pyridine analogs that contain varying substituents about the heterocycle core. As illustrated in Figure 8, eqs 1−8, a range of substituted mono- and bicyclic pyridines is easily accessible from the Ti-mediated reductive cross-coupling/cyclization sequence of aromatic and aliphatic aldehydes with suitably functionalized allylic alcohols. Overall, the substituted pyridine products from this process contain additional heteroaromatics [i.e., thiophenes (**39**, **44**, and **47**) and furans (**41**)], electron-rich and electron-poor
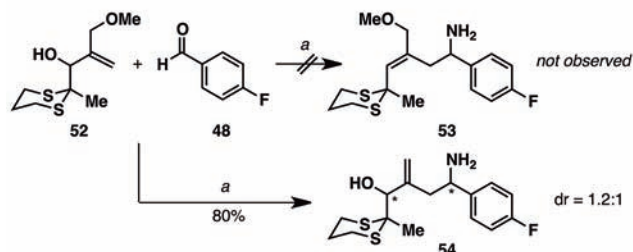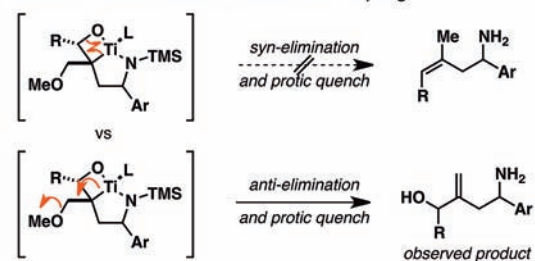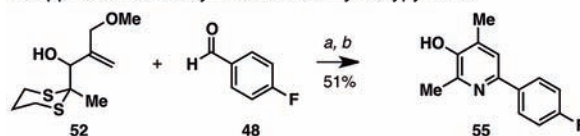

Figure 9. A pathway to 3-hydroxypyridines: (a) aldehyde (2 equiv), LiHMDS, Et₂O, then Ti(Oi-Pr)₄, c-C₅H₉MgCl, and then add Li-alkoxide of allylic alcohol (1 equiv); (b) HgO, BF₃·OEt₂, HCl, and THF (100 °C).

aromatics [including arylfluorides (**49**) and arylchlorides (**51**)] as well as aliphatic groups (**43**) and fused ring systems (**46**, **47**, and **49**).

In an attempt to expand the scope of this process to include heteroatom-substituted pyridine products, we have discovered a novel mode of reactivity associated with the Ti-mediated reductive cross-coupling process. As depicted in Figure 9A, coupling of aldehyde **48** with allylic alcohol **52** does not deliver the expected product of reductive cross-coupling **53**. Rather, convergent union delivers the 1,4-amino alcohol product **54** in 80% yield (as a 1.2:1 mixture of stereoisomers).[15] This surprising result is rationalized by the empirical model depicted in Figure 9B. Directed carbometalation ensues to deliver a fused bicyclic azametallacycle that has the potential to eliminate by either *syn*-elimination (as expected) or *anti*-elimination of the methyl ether. It is this latter pathway that is thought to result in the unexpected product **54**. While not a central focus of this study, we are quite interested in this alternative reaction pathway for metallacycle-mediated reductive cross-coupling and anticipate further study outside of the context of our interest in pyridine synthesis. Nevertheless, this surprising observation regarding the course of reductive cross-coupling, this process serves as a suitable entry to 3-hydroxypyridines, as depicted in Figure 9C.

3. CONCLUSION

Overall, we report a convergent de novo pyridine synthesis that proceeds via metallacycle-mediated union of readily available allylic alcohols and aldehydes. Our successes in these studies have defined a particularly powerful entry to this heterocyclic motif that appears well suited for the synthesis of pyridines bearing a great variety of substitution pattern. Unlike established

metallacycle-mediated pathways to pyridines that proceed by [2 + 2 + 2] annulation, the current contribution defines a regiospecific approach to the synthesis of differentially functionalized systems.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and tabulated spectroscopic data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

■ REFERENCES

(1) For a recent review, see: Henry, G. D. *Tetrahedron* **2004**, *60*, 6043−6061.

(2) *Name Reactions in Heterocycle Synthesis*; Li, J. J., Corey, E. J., Eds; Wiley: New York, 2005; p 558.

(3) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592−4593.

(4) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918−6919.

(5) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645−3651.

(6) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602−8603.

(7) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096−10097.

(8) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781−793.

(9) (a) Donohoe, T. J.; Fishlock, L. P.; Basutto, J. A.; Bower, J. F.; Procopiou, P. A.; Thompson, A. L. *Chemical Commun.* **2009**, 3008−3010. (b) Donohoe, T. J.; Basutto, J. A.; Bower, J. F.; Rathi, A. *Org. Lett.* **2011**, *13*, 1036−1039.

(10) For a review, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556.

(11) For a Ti(O*i*-Pr)$_4$-mediated regioselective route to pyridines by [2 + 2 + 2] between a terminal alkyne, internal alkyne, and nitrile, see: (a) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518−3519. (b) Suzuki, D.; Nobe, Y.; Watai, Y.; Tanaka, R.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7474−7479. For a recent review of Cp$_2$Zr-mediated [2 + 2 + 2] for pyridine synthesis, see: (c) Zhou, L.; Yamanaka, M.; Kanno, K.; Takahashi, T. *Heterocycles* **2008**, *76*, 923−947.

(12) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 9216−9219.

(13) For a review of Ti(II)-mediated conversion of dithioacetals to Ti carbene complexes, see: Takeda, T. *Chem. Rec.* **2007**, *7*, 24−36.

(14) For a detailed discussion of stereoselectivity in metallacycle-mediated allylic alcohol−imine coupling, see: Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Umemura, S.; Micalizio, G. C. *J. Org. Chem.* **2010**, *75*, 8048−8059.

(15) The stereochemistry of these isomers was not assigned.