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Redox Cycloisomerization Approach to 1,2-Dihydropyridines

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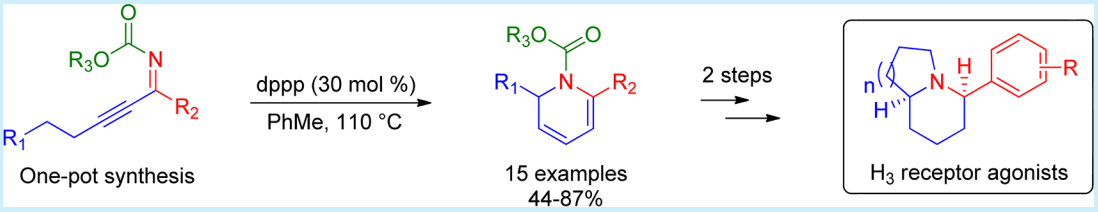
Supporting Information



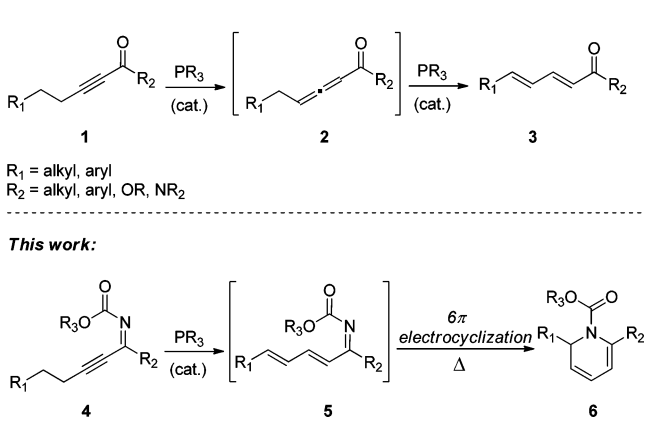
ABSTRACT: The phosphine-catalyzed synthesis of 1,2-dihydropyridines via an alkyne isomerization/electrocyclization sequence is described. Propargylidenecarbamate substrates were prepared following a *one-pot* procedure between a terminal alkyne, a benzonitrile, and a chloroformate in the presence of trimethylaluminum. This methodology gives access to a diverse set of 2,6-disubstituted 1,2-dihydropyridines in high yield. The products can be easily converted into substituted piperidines or pyridines, and this methodology was applied to the synthesis of indolizidines.

Heterocycles containing nitrogens are found abundantly in a broad array of natural products and pharmaceutically active substances.[1] Thus, an important amount of therapeutic agents contains polysubstituted piperidine or pyridine scaffolds.[2] They are also important precursors to complex biologically active molecules and are frequently utilized as building blocks.[3] As a result, numerous methods have been reported for the synthesis of substituted piperidines[4,5] and pyridines.[5]

1,2-Dihydropyridines are extremely useful and reactive synthetic intermediates, as they can easily give access to a large variety of polysubstituted 6-membered N-heterocycles.[5−7] In comparison to 1,4-dihydropyridines, relatively few general methods for their selective synthesis have been reported in the literature rendering 1,2-dihydropyridines as underutilized chemical intermediates by the synthetic community.[6] Major reasons are the poor stability upon storage of 1,2-dihydropyridines having no withdrawing group at the nitrogen atom and the fact that most reported syntheses give a limited product scope along with the formation of 1,4-dihydropyridines as side products.[6] Traditional ways to prepare 1,2-dihydropyridines include pyridinium salt dearomatization via addition of Grignard[8] or organocuprate reagents[9] as well as pericyclic reactions.[6] Ellman and co-workers reported the Rh-catalyzed addition of alkynes to α,β-unsaturated *N*-benzyl aldimines via C−H activation followed by 6π-electrocyclization.[10] Similarly, Okamura and co-workers described the 6π-electrocyclization of 1-azatrienes prepared from primary amines and 2,4-dienals.[11−13] These approaches are highly efficient and occurred under mild conditions but remain limited to alkyl imines. Thus, while the importance of accessing 6-membered nitrogen containing rings via 1,4-dihydropyridines (Hantzsch reaction) is well demonstrated,[7,14] having available a corresponding reaction via selective 1,2-dihydropyridines would open complementary regioselectivity in further derivatization as well as constitute a new approach to pyridines.

We previously reported the isomerization of electron-poor alkynes **1** to dienes **3** catalyzed by nucleophilic phosphines.[15,16] Alkynones,[16] alkynoates,[16] and alkynamides[17] were efficiently isomerized to the corresponding (*E,E*)-1,3-diene products which proceed through the formation of an allene intermediate **2** (Scheme 1). As part of our ongoing program aimed at creating structural complexity by catalytic isomerization of readily available unsaturated molecules,[18] we now report the isomerization of propargylidenecarbamates **4** to 1,3-dienimines **5** followed by 6π-electrocyclization to obtain 1,2-dihydropyridines **6**.

Scheme 1. Phosphine-Catalyzed Isomerization of Alkynes to 1,3-Diene



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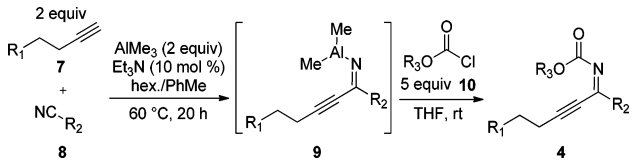
In order to increase the synthetic utility of this methodology, we first investigated an efficient route to access unprecedented protected ynimines **4**. Following a modified procedure recently reported by Lee and co-workers, we found that ynimines **4** could be easily accessed utilizing a *one-pot* procedure illustrated in Scheme 2.[19] Nonenaminizable substrates **4** were prepared in

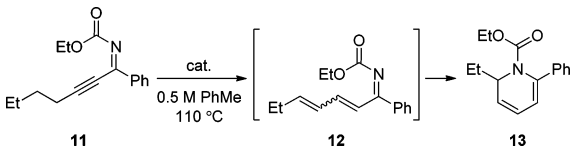
Scheme 2. One-Pot Substrate Synthesis



good to high yields by addition of alkynyldimethylaluminum reagents (generated *in situ* by reaction of $AlMe_3$ with a terminal alkyne) to nitrile **8** in hexanes/toluene followed by addition of the desired chloroformate **10** to dimethylaluminum iminate intermediate **9**.[20]

To test our hypothesis concerning the conversion of **4** to **6**, different phosphine donors were screened under various reaction conditions. Initial experiments with triphenylphosphine as catalysts in toluene gave full conversion but low isolated yields, and significant decomposition was observed (Table 1, entries 1 and 2). The use of more nucleophilic phosphines increased the amount of decomposition products, and only low amounts of **13** were obtained (entries 3 and 4).

Table 1. Selected Phosphine Optimization



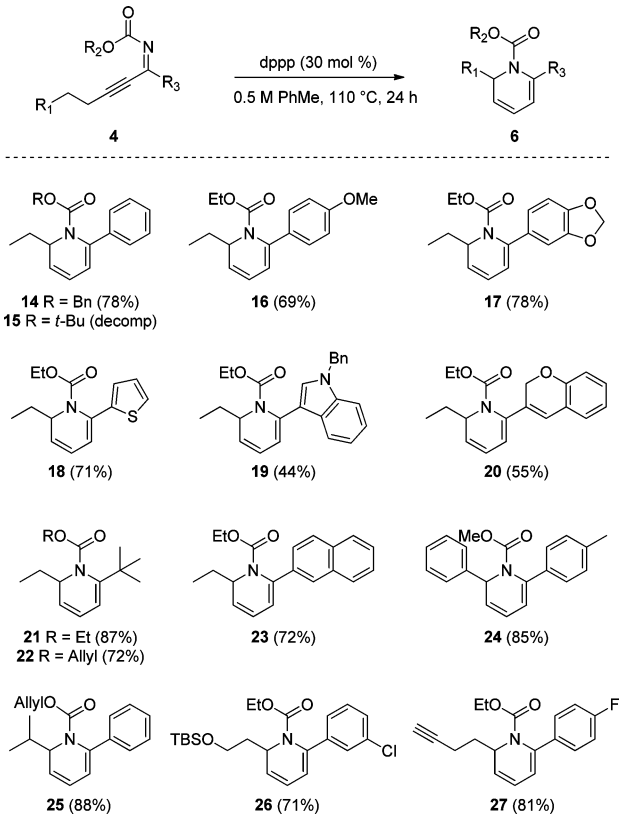
entry	cat. (mol %)[a]	time (h)	conv (%)	yield (%)[b]
1	PPh_3 (30)	48	100	21
2	PPh_3 (50)	48	100	33
3	Ph_2PMe (30)	24	100	–[c]
4	$Ph_2PAllyl$ (30)	24	85	20
5	dppp (10)	48	80	10[c]
6	dppp (30)	24	100	76
7[d]	dppp (30)	16	100	<10[e]
8	dppp/AcOH (30)	1	100	–[f]
9	dppp/$(PhS)_2$ (30/10)	16	30	<5
10	dppe (30)	24	80	34
11	dppf (30)	16	100	<10[c]

[a]dppp: bis(diphenylphosphino)propane; dppe: bis(diphenylphosphino)ethane; dppf: 1,1′-bis(diphenylphosphino)ferrocene. [b]Isolated yield. [c]Complex mixture of products. [d]Reaction performed at 80 °C. [e]Full conversion to diene **12** was determined by ^1H NMR spectrum analysis of the crude material. [f]Extensive decomposition was observed.

Next we decided to explore the use of bidentate phosphines in the reaction. Their advantage can be explained by the ability of the second phosphine to act as a base[16b] and therefore to promote proton transfer within the diene chain. Gratifyingly, bidentate phosphine dppp (30 mol %) gave the desired 1,2-dihydropyridine **13** in 76% yield after 24 h at 110 °C (entry 6). The difference in reactivity between dppp and dppe (entries 6 and 10) remains unclear but suggests that the second phosphine of dppe does not promote proton transfer, as similar results were obtained when monodentate allyldiphenylphosphine was used (entry 4). It is also noteworthy that **11** can easily isomerize to **12**[21] at lower temperature (80 °C) over 16 h but cyclization to **13** proved to be much slower.[22] We also investigated the addition of a proton source in a catalytic amount, but **11** rapidly decomposed above 60 °C under acidic conditions (entry 8).

With these optimized conditions in hand, we investigated the product scope of this new cascade phosphine-catalyzed isomerization/6π-electrocyclization transformation (Scheme 3). To our delight, products **6** can be isolated in high yield

Scheme 3. Product Scope



starting from **4** with a large range of substituent patterns. The reaction tolerates the presence of functional groups present in various molecules of biological interest such as piperonyl (**17**), thiophene (**18**), indole (**19**), and benzopyran (**20**). We also screened different carbamates that could be easily removed, thus adding synthetic versatility to the products. The reaction proceeds well to give benzyl (**14**), allyl (**22** and **25**), ethyl, and methyl carbamates of dihydropyridines; however, *tert*-butyl carbamate (**15**) was not obtained, as slow decomposition of the starting material was observed, presumably due to steric hindrance proximal to the alkyne moiety and slow thermal removal of the Boc group.

The alkyl chain was also successfully functionalized with different types of substituents. Interestingly, this reaction tolerated a large variety of synthetically useful functional groups such as terminal alkyne **27** and silyl protected alcohol **26**.

To further explore the synthetic utility of 1,2-dihydropyridine scaffolds, we investigated the functionalization of the 3,5-diene

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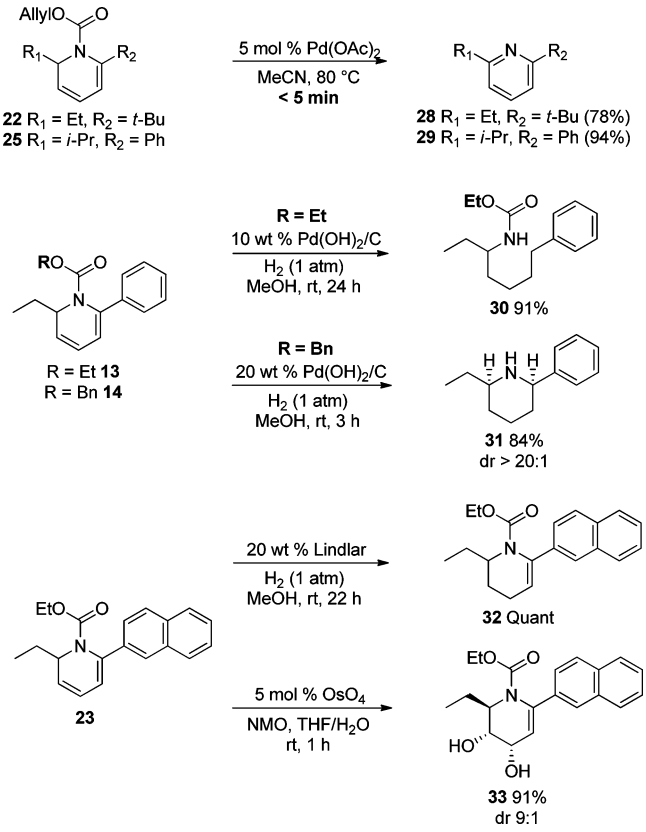
moiety. First, oxidation of various protected 1,2-dihydropyridines to pyridines was attempted under various reaction conditions (2,3-dichloro-5,6-dicyanobenzoquinone, *o*-chloranil, and $Mn(OAc)_2$).[23] Unexpectedly, **6** reacted poorly and decomposed when reactions were run at higher temperature. Therefore, we envisioned a nonoxidative approach which would best suit our needs to access substituted pyridines. To the best of our knowledge, Pd-catalyzed deallylation/β-hydride elimination of allyl vinylcarbamate to vinyl imine has not been reported. We hypothesized that the β-hydride elimination should be highly favored in the case of a 1,2-dihydropyridine. Satisfyingly, when **22** and **25** were treated with a catalytic amount of $Pd(OAc)_2$ as a convenient precatalyst for Pd(0) in MeCN at 80 °C, pyridines **28** and **29** were obtained in excellent yield (Scheme 4). This reaction performed without any phosphine ligand in contrast to Tsuji's conditions for his decarboxylative dehydrogenation of allyl β-ketoesters.[24]

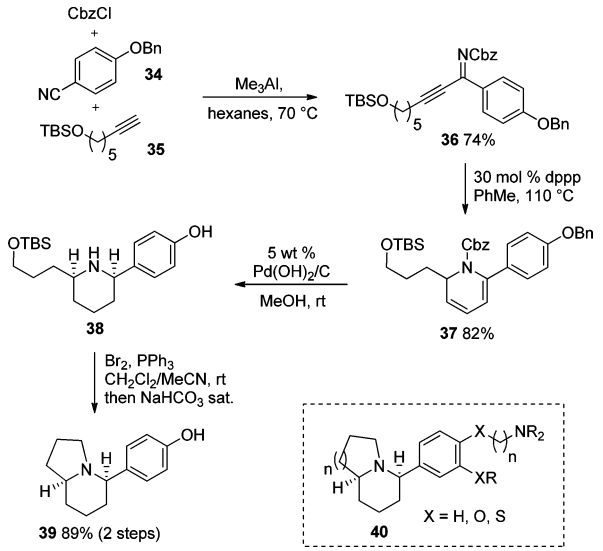
Scheme 4. Synthetic Applications



Depending on the nature of the carbamate, different levels of hydrogenation could be achieved in the presence of molecular hydrogen and Pearlman's catalyst. Rapid removal of the Cbz group favored formation of piperidine *cis*-**31** with excellent yield and *dr*, whereas the presence of ethylcarbamate facilitated hydrogenolysis of **13** to give **30**. We were also able to selectively and quantitatively hydrogenate the olefin at the 3,4-positions of the 1,2-dihydropyridine system using Lindlar's catalyst to give **32**. It should also be noted that the diene offers an opportunity to further functionalize the ring carbons. For example, chemo- and diastereoselective dihydroxylation of **23** provides **33** in 9:1 dr.

To demonstrate the synthetic utility of this new methodology, we investigated a synthesis of indolizidine **39** (Scheme 5).[25] Starting from readily available nitrile **34**, terminal alkyne **35**, and CbzCl, 1,2-dihydropyridine **37** was easily obtained in

Scheme 5. Concise Synthesis of Indolizidine 39



two steps using the transformation reported herein. Dihydropyridine **37** was hydrogenated in the presence of 5 wt % of $Pd(OH)_2/C$ to give *cis*-piperidine **38**. Finally a *one-pot* bromination[26]/cyclization gave **39** in high yield (89%). In just four steps, we were able to access compound **37**, which is a useful synthetic intermediate for the preparation of the histamine H_3 receptor agonists **40**, used for treatment of pain and sleeping disorders.[25,27]

In summary, we have developed an efficient synthesis of 1,2-dihydropyridines starting from propargylidenecarbamates catalyzed by bisphosphine dppp. Protected propargyl imines **4** were prepared in a *one-pot* procedure from commercially available reagents. The transformation proved to be high yielding and provided easy access to motifs found in molecules of biological interest. We also reported useful functionalizations of the reactive 1,2-dihydropyridine core structure to synthesize piperidine, pyridine, or noncyclic carbamates. The applicability of the method has also been demonstrated by a concise synthesis of indolizidine **39**.

■ ASSOCIATED CONTENT

Supporting Information

Experiment details, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Synthesis of enaminizable propargylidenecarbamate substrates was unsuccessful.

(21) Formation of **12** can be monitored by thin layer chromatography.

(22) We also investigated the *cis*−*trans* isomerization of diene **12** in the presence of Ph_2S_2 (Table 1, entry 9), but only a trace of **13** was observed.

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