Homogeneous Catalysis

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Stereoselective Phosphine-Catalyzed Synthesis of Highly Functionalized Diquinanes**

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In 2003, Tomika and co-workers reported an intriguing P*n*Bu$_3$-catalyzed diastereoselective cyclization of certain yne-diones to form bicyclic furanones with two new stereocenters (Figure 1).[1] They proposed that conjugate addition of

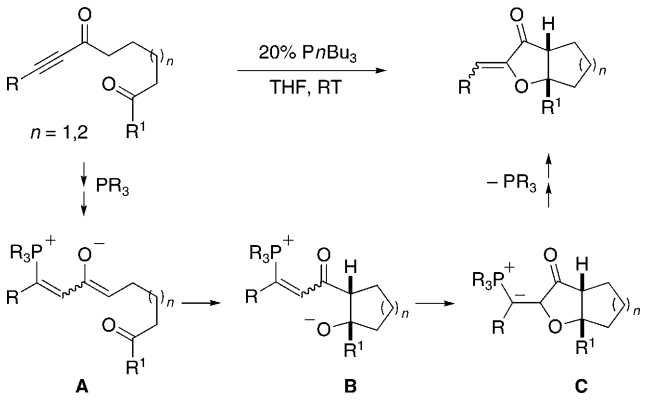
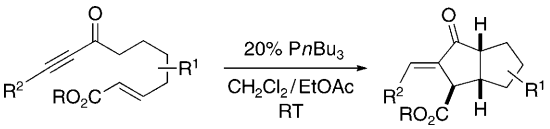


Figure 1. The phosphine-catalyzed reaction of yne-diones to form bicyclic furanones (for simplicity, the steps are drawn as being irreversible).

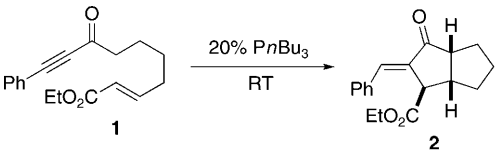
the phosphine to the alkyne is followed by tautomerization, which furnishes zwitterionic enolate **A**. Next, an intramolecular aldol reaction provides **B**, and then a second conjugate addition generates bicycle **C** (the conversion of **A** into **C** by a concerted cycloaddition may also be considered). Tautomerization and then elimination of the phosphine affords the bicyclic furanone. The investigation by Tomita et al. focused mainly on symmetrical substrates ($R^1 = -C \equiv CR$), although they did report reactions of two unsymmetrical yne-diones which cyclized in relatively modest yield (41–50%).

The study by Tomita et al.[1] provided an excellent illustration of how the use of a nucleophilic catalyst can open the door to new modes of reactivity.[2] Surprisingly, to the best of our knowledge, there have been no subsequent investigations that further develop this interesting reaction manifold (that is, conjugate-addition/cross-tautomerization to generate a dipolar intermediate such as **A**). Herein, we exploit this reactivity to achieve the phosphine-catalyzed diastereoselective transformations of acyclic precursors into highly functionalized diquinanes that bear multiple (three or four) contiguous stereocenters [Reaction (1)].[3]



(1)

Not only are diquinanes (including bicyclo[3.3.0]octan-2-ones) subunits of a wide array of bioactive compounds, but they are also versatile intermediates in organic synthesis.[4,5] We envisioned that a phosphine-catalyzed method for the generation of such structures might be viable (Krische et al. have also developed a powerful phosphine-catalyzed approach to the synthesis of diquinanes[6]) if a zwitterion derived from **1** (analogous to **A** in Figure 1) could be induced to undergo an intramolecular Michael addition rather than an aldol reaction. Unfortunately, when subjected to the conditions developed by Tomita et al., compound **1** was only transformed into the target diquinane in very low yield [<10%; Reaction (2)].



(2)

Solvent	Yield
THF (0.5 M)	<10%
CH_2Cl_2/EtOAc (9:1; 0.01 M)	89% (>20:1 d.r.)

Upon investigating a variety of reaction parameters, such as catalyst, temperature, solvent, and concentration, we found that the desired reaction manifold could be obtained through an appropriate choice of solvent and concentration. Thus, by conducting the cyclization in CH_2Cl_2/EtOAc (9:1) under more dilute conditions, we can efficiently generate the target diquinane, which bears three new contiguous stereocenters and an *E* double bond, as a single diastereomer [89% yield; Reaction (2)].[7]

This phosphine-catalyzed reaction can be applied to the stereoselective synthesis of an array of diquinanes; in each

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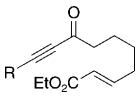
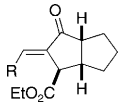
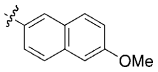
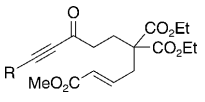
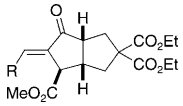
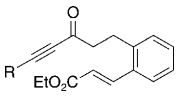
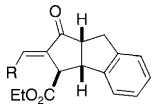
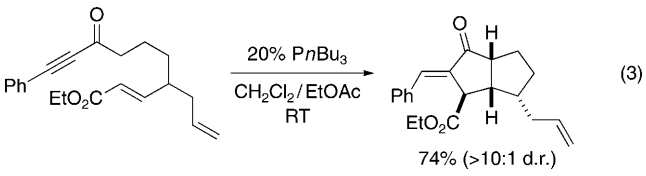
Table 1: The stereoselective phosphine-catalyzed synthesis of highly functionalized diquinanes at room temperature (20% P*n*Bu$_3$, CH_2Cl_2/EtOAc).

Entry	Substrate	Product	Yield [%][a]
1		R = Ph 	89
2			83
3		cyclohex-1-enyl	84
4[b]		Cy	45
5		R = Ph 	88
6		cyclohex-1-enyl	88
7		Cy	74
8		*n*Bu	77
9		Me	56
10		R = Ph 	88
11		*n*-pentyl	54

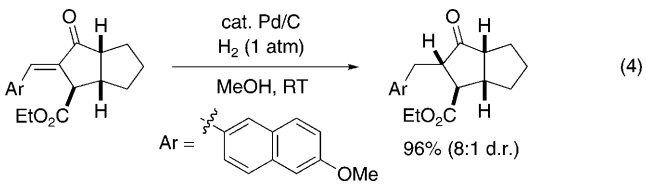
[a] Yield of purified product (average of two experiments). All diastereomeric ratios are > 20:1. [b] 1.0 equivalents of P*n*Bu$_3$ were used.

case, a single diastereomer is produced (Table 1).[8] For example, the alkyne subunit can be furnished with an aromatic, alkenyl, or alkyl group (R, Table 1); the ability to achieve cyclizations of alkyl-substituted compounds (Table 1, entries 4, 7, 8, and 11) is noteworthy, as β-alkyl-substituted ynones are susceptible to phosphine-catalyzed isomerization to conjugated dienones.[9] The linker between the ynone and the enoate can bear substituents (e.g. Table 1, entries 5–9) or even include an aromatic ring (Table 1, entries 10 and 11). Furthermore, an existing stereocenter can control the stereochemistry of the three newly created stereocenters [Reaction (3)].

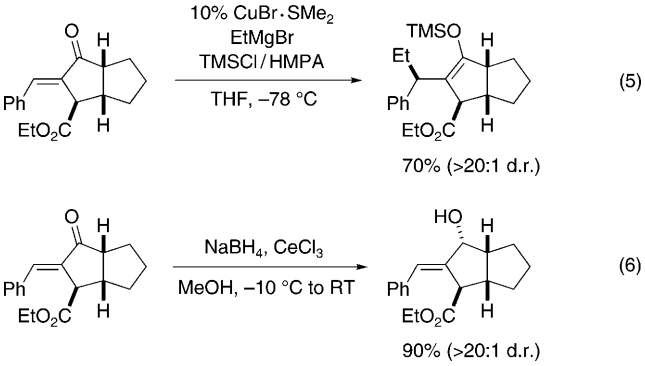


(3)

The diquinanes produced using this phosphine-catalyzed double-cyclization process can be functionalized with a high degree of stereoselectivity. Thus, new stereocenters can be introduced on the α or β positions of the enone [Reaction (4) and Reaction (5)],[10] as well as on the carbonyl group itself [Reaction (6)].



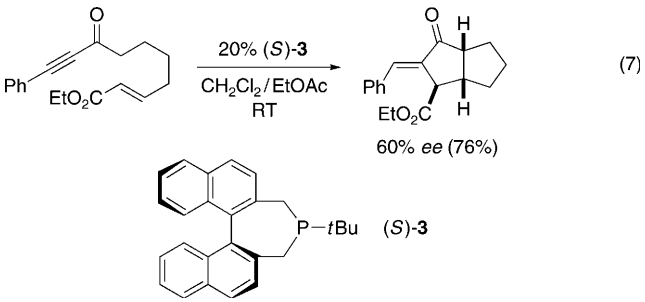
(4)



(5)

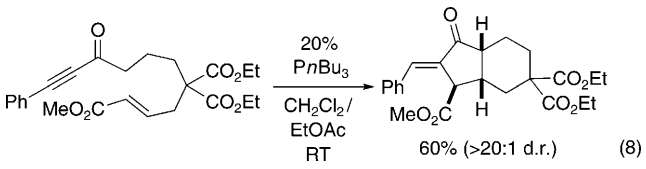
(6)

We are developing an enantioselective variant of this phosphine-catalyzed diquinane synthesis. We anticipated that this might be comparatively challenging, owing to issues such as the potential generation of mixtures of *E*/*Z* isomers in key intermediates and the distance between the phosphine subunit and the site(s) of carbon–carbon bond formation. In view of such complications, we were pleased to find that phosphepine **3** can catalyze the synthesis of a diquinane with promising enantioselectivity [60% *ee*; Reaction (7)].[11–13]

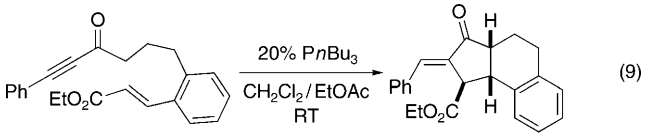


(7)

We have begun to explore the application of this procedure to the synthesis of other classes of fused carbocycles. Hydrindanes are an important family of targets,[14] and in a preliminary study we have found that, without further optimization, the procedure that we developed for the formation of diquinanes can be employed for the generation of 6,5 ring systems in promising yields and excellent stereoselectivities [Reaction (8) and Reaction (9)].



60% (>20:1 d.r.) (8)



(9)

72% (>20:1 d.r.)

In summary, building on a powerful but largely unexploited mode of reactivity discovered by Tomita et al.[1] (phosphine catalysis by initial conjugate addition followed by cross-tautomerization of an unsaturated carbonyl compound), we have developed a versatile new method for the room-temperature synthesis of diquinanes from acyclic precursors, thereby generating two rings, three stereocenters, and a double bond with high selectivity. The products of the double cyclization can be derivatized with excellent diastereoselection into an array of highly functionalized compounds. From the preliminary studies, we suspect that an enantioselective variant can be achieved and that this method can be applied to the synthesis of other fused ring systems. Future investigations within the group will continue to explore the scope of novel modes of reactivity furnished by phosphines and other nucleophilic catalysts.

Experimental Section

General procedure: A flask charged with the substrate was evacuated and refilled with argon three times. The appropriate volume of CH_2Cl_2:EtOAc (9:1) was added to afford a 0.01M solution of the substrate. P*n*Bu_3 (0.20 equiv) was added by syringe, and the solution was stirred for 20 h at room temperature. The reaction mixture was then exposed to air for 1 h, filtered through a short pad of silica gel with Et_2O washings (100 mL), and concentrated. The desired product was obtained by flash chromatography.

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[6] J.-C. Wang, S.-S. Ng, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683. This method proceeds best at 110°C and is not effective for the synthesis of hydrindanes ("*dramatically reduced diastereoselectivities and yields*").
[7] At higher concentrations, intermolecular processes appear to predominate; other solvents (e.g., Et_2O, toluene, and chloroform) and other potential catalysts (e.g., PMe_3, PCy_3, $P(anisyl)_3$, and NEt_3) are less effective.
[8] Under our standard conditions, formation of the desired diquinane is not observed when R = H or Si(*t*Bu)Me_2 (Table 1) or when the ester is replaced with a ketone. According to ^{31}P NMR spectroscopy, the free phosphine, not a phosphonium-ion intermediate, is the resting state of the catalyst during the diquinane-forming process.
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[13] The absolute stereochemistry of the product has not yet been determined.
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