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Phosphine-Catalyzed Stereoselective Synthesis of Highly Functionalized Diquinanes**

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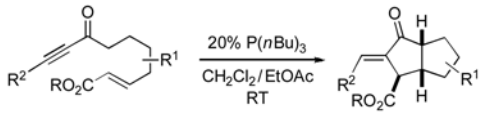
In 2003, Tomita reported an intriguing P(*n*-Bu)$_3$-catalyzed diastereoselective cyclization of certain yne-diones to form bicyclic furanones that bear two new stereocenters (Figure 1).[1] He proposed that conjugate addition of the phosphine to the alkyne is followed by tautomerization, which furnishes zwitterionic enolate **A**. Next, an intramolecular aldol reaction provides **B**, and then a second conjugate addition generates bicycle **C** (the conversion of **A** to **C** via a concerted cycloaddition may also be considered). Tautomerization and then elimination of the phosphine affords the bicyclic furanone. Tomita's investigation focused on symmetrical substrates (i.e., R^1 = –C≡CR), although he did report reactions of two unsymmetrical yne-diones, which cyclized in relatively modest yield (41–50%).

This study by Tomita provides 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 (i.e., conjugate-addition/cross-tautomerization to generate a dipolar intermediate such as **A**). In this report, we exploit this reactivity to achieve phosphine-catalyzed diastereoselective transformations of acyclic precursors into highly functionalized diquinanes that bear multiple (three or four) contiguous stereocenters [Eq. (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 has 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, rather than an aldol, reaction.

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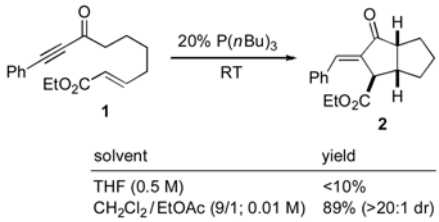
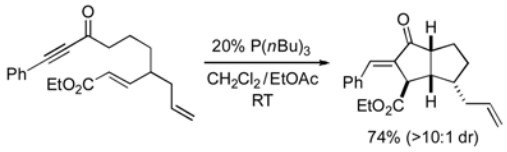
Unfortunately, when subjected to the conditions developed by Tomita, compound **1** was not transformed into the target diquinane in significant yield [<10% yield; Eq. (2)].



(2)

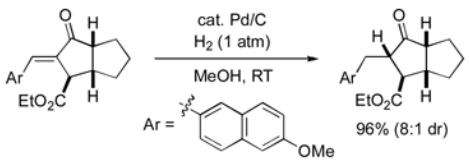
Upon investigating a variety of reaction parameters (e.g., catalyst, temperature, solvent, and concentration), we determined that the desired reaction manifold can be achieved through the appropriate choice of solvent and concentration. Thus, by conducting the cyclization in CH_2Cl_2/EtOAc (9/1) under 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; Eq. (2)].[7]

This phosphine-catalyzed reaction can be applied to the stereoselective synthesis of an array of diquinanes (Table 1; in each case, a single diastereomer is produced).[8] For example, the alkyne subunit can include an aromatic, alkenyl, or alkyl group (see R in Table 1); the ability to achieve cyclizations of alkyl-substituted compounds (entries 4, 7, 8, and 11) is noteworthy, since 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., entries 5–9) or include an aromatic ring (entries 10 and 11). Furthermore, an existing stereocenter can control the stereochemistry of the three newly created stereocenters [Eq. (3)].

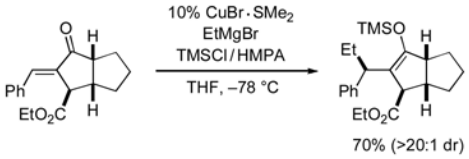


(3)

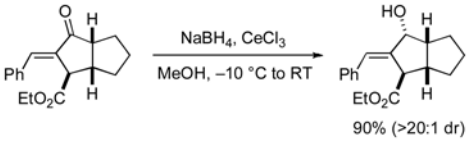
The diquinanes produced via our phosphine-catalyzed double cyclization process can be functionalized with high stereoselectivity. Thus, new stereocenters can be introduced at the α or the β position of the enone [Eq. (4) and Eq. (5)],[10] as well as at the carbonyl group itself [Eq. (6)].



(4)

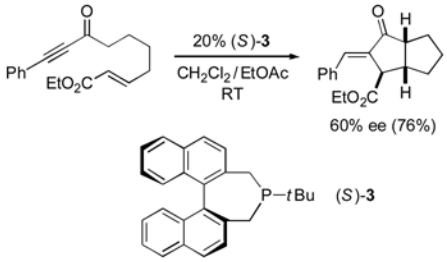


(5)



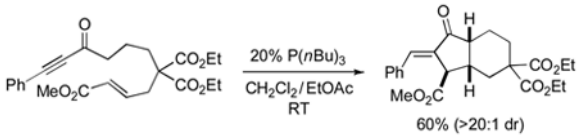
(6)

We have initiated an investigation of an enantioselective variant of this phosphine-catalyzed diquinane synthesis. We anticipated that this challenge might be comparatively difficult, due 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 determine that phosphepine **3** can catalyze the synthesis of a diquinane with promising enantioselectivity [60% ee; Eq. (7)].[11,12,13]

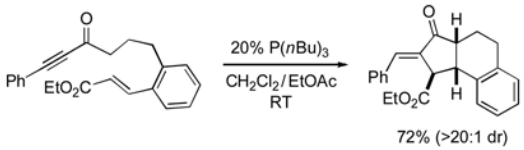


(7)

We have begun to explore the application of our method to the synthesis of other classes of fused carbocycles. Hydrindanes are an important family of targets,[14] and in a preliminary study we have determined that, without separate optimization, the method that we developed for the formation of diquinanes can be employed for the generation of 6,5 ring systems with promising yield and excellent stereoselectivity [Eq. (8) and Eq. (9)].



(8)



(9)

In summary, building on a powerful but largely unexploited mode of reactivity discovered by Tomita (phosphine catalysis via conjugate addition then 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 an olefin with high selectivity. The products of the double cyclization can be derivatized with excellent diastereoselection into an array of highly functionalized compounds. Preliminary studies suggest that an enantioselective variant can be achieved and that the method can be applied to the synthesis of other fused ring systems. Future investigations will further explore the scope of novel modes of reactivity furnished by phosphines and other nucleophilic catalysts.

Experimental Section

General procedure

A flask was charged with the substrate, and then it was evacuated and refilled with argon three times. The appropriate volume of CH_2Cl_2:EtOAc (9:1) was added to afford a 0.01 M 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. Then, the reaction mixture was 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 purified by flash chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Kuroda H, Tomita I, Endo T. Org Lett. 2003; 5:129–131. [PubMed: 12529122]
2. For reviews and leading references to nucleophilic catalysis by phosphines, see: Methot JL, Roush WR. Adv Synth Catal. 2004; 346:1035–1050.Ye LW, Zhou J, Tang Y. Chem Soc Rev. 2008; 37:1140–1152. [PubMed: 18497927] Lu X, Zhang C, Xu Z. Acc Chem Res. 2001; 34:535–544. [PubMed: 11456471]
3. For our earlier studies of nucleophilic catalysis by phosphines, see: Wurz RP, Fu GC. J Am Chem Soc. 2005; 127:12234–12235. [PubMed: 16131196] Wilson JE, Fu GC. Angew Chem, Int Ed. 2006; 45:1426–1429.Chung YK, Fu GC. Angew Chem, Int Ed. 2009; 48:2225–2227.Smith SW, Fu GC. J Am Chem Soc. accepted.
4. For reviews that include leading references to the synthesis of diquinanes, as well as examples of natural products that include a bicyclo[3.3.0]octan-2-one ring system, see: Mehta G, Srikrishna A. Chem Rev. 1997; 97:671–719. [PubMed: 11848885] Singh V, Thomas B. Tetrahedron. 1998; 54:3647–3692.
5. For a few examples of the use of bicyclo[3.3.0]octan-2-ones as intermediates in natural-product synthesis, see: Wrobleski A, Sahasrabudhe K, Aubé J. J Am Chem Soc. 2002; 124:9974–9975. [PubMed: 12188646] Winkler JD, Rouse MB, Greaney MF, Harrison SJ, Jeon YT. J Am Chem Soc. 2002; 124:9726–9728. [PubMed: 12175229] Yang J, Long YO, Paquette LA. J Am Chem Soc. 2003; 125:1567–1574. [PubMed: 12568617]

6. Wang JC, Ng SS, Krische MJ. 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"). [PubMed: 12656582]
7. Notes: a) At higher concentration, intermolecular processes appear to predominate; b) 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. Notes: a) 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; b) 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.
9. Trost BM, Kazmaier U. J Am Chem Soc. 1992; 114:7933–7935. The dienone, when formed, is not converted into the diquinane under our conditions.
10. Matsuzawa S, Horiguchi Y, Nakamura E, Kuwajima I. Tetrahedron. 1989; 45:349–362.
11. Phosphepine **3** was originally developed as a chiral ligand for transition metal-catalyzed reactions. For the initial report, see: Chi Y, Zhang X. Tetrahedron Lett. 2002; 43:4849–4852.
12. More recently, phosphepine **3** has been employed as a chiral nucleophilic catalyst. For early reports, see References 3a and 3b.
13. The absolute stereochemistry of the product has not yet been determined.
14. For some examples of natural products that include a cis-hydrindane subunit, see: Trost BM, Haffner CD, Jebaratnam DJ, Krische MJ, Thomas AP. J Am Chem Soc. 1999; 121:6183–6192.

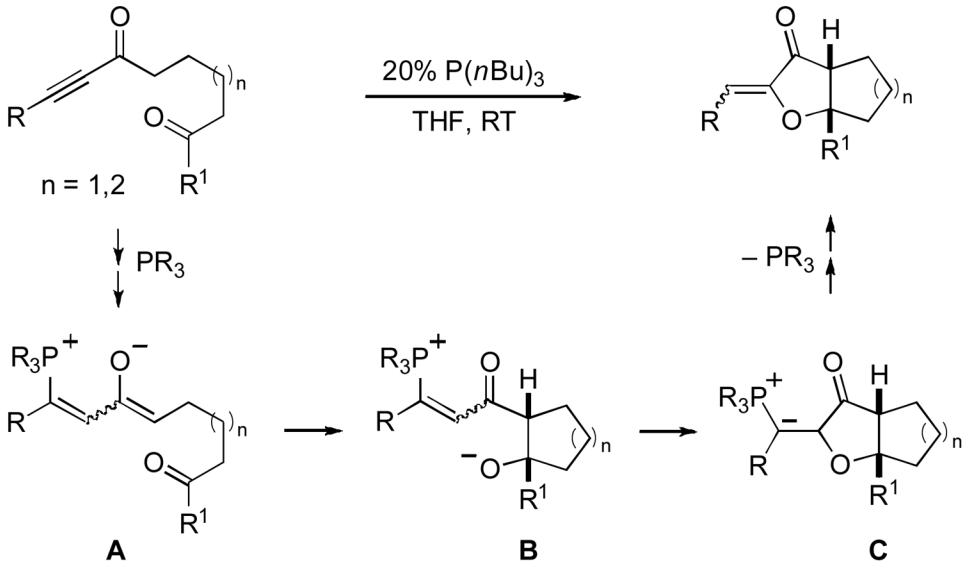
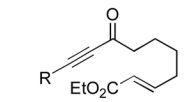
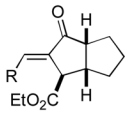
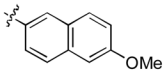
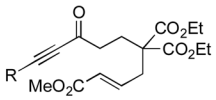
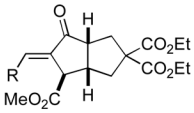
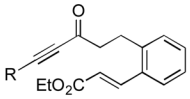
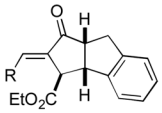


Figure 1.
Phosphine-catalyzed reaction of yne-diones to form bicyclic furanones (for the sake of simplicity, the steps are drawn as irreversible).

Table 1

Phosphine-catalyzed stereoselective 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 dr's are >20:1.

[b] 1.0 equiv P(*n*-Bu)3 was used.