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AROMATIC ANNELATION; APPLICATION TO THE SYNTHESIS OF UNSYMMETRICAL BIPHENYLS.

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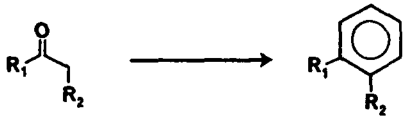
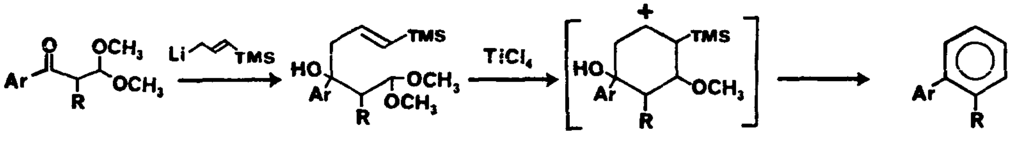
Summary: A procedure for the preparation of unsymmetrical biphenyls by elaboration of aromatic rings from aryl alkyl ketones is described.

The formation of cyclic products from acyclic precursors is an important objective in organic synthesis. Ring forming reactions play a prominent role in the total synthesis of natural products. Although diverse methods for the elaboration of 6-membered carbocycles exist, to date there is a lack of methodology for converting an α-methylene ketone to the corresponding aromatic ring (equation 1). Modifications of the Diels-Alder reaction and the Robinson annelation for the preparation of substituted aromatics and phenols from aliphatic precursors have been published.[1] A synthesis of phenyl rings using a cationic cyclization and its application to the preparation of unsymmetrical biphenyls will be described in this note.[2]



(1)

The impetus for this study was provided by our early observation of C=C participation during the acid catalyzed hydrolysis of β-propenyl α,β-unsaturated acetals. Although the yields of aromatic products formed during this process were low, we predicted that a slight modification of the substrate would lead to improvement. The addition of allyltrimethylsilyllithium[3] at -78°C in tetrahydrofuran (THF) to ketoacetals 1 (equation 2) produced vinyl silanes

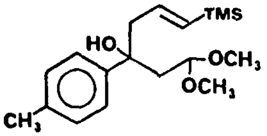
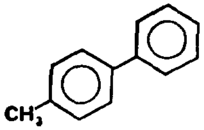
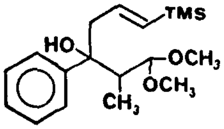
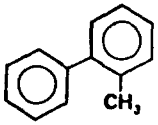
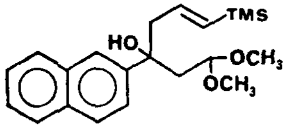
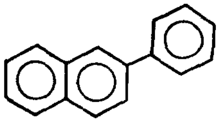
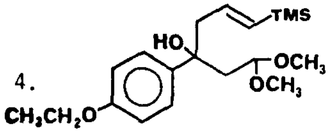
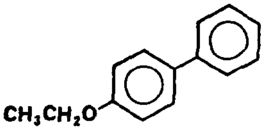
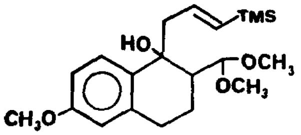
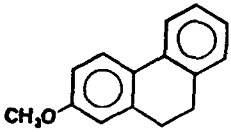


(2)

1 2 3 4

TMS : $(CH_3)_3Si$

Table I[a]

	Starting Material	Product	Isolated Yield[b]
1.			59% mp[c,d] 47-48°C
2.			44%
3.			53% mp[c,e] 95-96°C
4.			49% mp[c] 72-73°C
5.			12%

(a) All materials gave satisfactory ir, ^{1}H nmr and mass spectra.

(b) Yields refer to products purified by column chromatography.

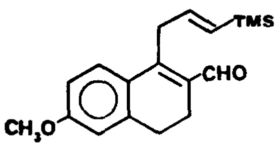
(c) Melting points were determined on sublimed samples and are not corrected.

(d) M. Gomberg and J. C. Pernert, J. Am. Chem. Soc., 48, 1372 (1926); m.p. 47.7°C

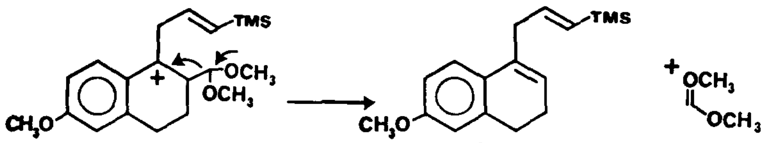
(e) M. Guyot and C. Mentzer, Bull. Soc. Chim. Fr., 1843 (1967); m.p. 102°C.

2 in 67-91% yield after column chromatography on silica gel. The ketoacetals were prepared in high yield from the corresponding ketones according to published procedures.[4] Treatment of the vinyl silanes 2 with titanium tetrachloride or stannic chloride in dichloromethane solution containing *ca.* 10% ether at -78°C followed by gradual warming to 0°C gave the biphenyl compounds 4 (See Table I).[5] Initial complexation of the Lewis acid with the acetal presumably is followed by intramolecular attack to form the stabilized carbonium ion 3. Subsequent loss of the elements of methanol and water leads to the observed product.

A variety of protic and Lewis acids were examined in an attempt to optimize the yield for this process. Boron trifluoride etherate, ethylaluminum dichloride, camphor-10-sulfonic acid, titanium tetraisopropoxide and titanium dichlorodiisopropoxide[6] were all found to be less effective than titanium tetrachloride. An interesting observation was made when the vinyl silane derived from 6-methoxy-1-tetralone (Table I, entry 5) was treated with perchloric acid at 23°C in aqueous THF. Equal amounts of the anticipated product, α,β-unsaturated aldehyde 5,



5



6 7

(3)

and of another compound, identified as olefin 6, were formed.[7] Evidently ionization of the tertiary alcohol takes place with subsequent fragmentation to give 6 and oxonium ion 7 (equation 3). This novel fragmentation did not take place during the Lewis and catalyzed reaction.

The utility of this short new procedure for the direct annelation of a phenyl ring onto an α-methylene ketone has been demonstrated by the examples cited in Table I. Experimental details follow.

4-Methylbiphenyl: A solution of 270 mg of the vinyl silane precursor (Table I, entry 1) in a minimum amount of dry methylene chloride was transferred by cannula to a stirred solution of 280 μl (3 equiv) of titanium tetrachloride in 8 ml of methylene chloride and 0.8 ml of ether at -78°C (Argon atmosphere). The solution was stirred at this temperature for 0.5 h and was subsequently allowed to warm to 0°C during *ca.* 4 h. The reaction mixture was poured onto sodium bicarbonate solution and ice, filtered to remove the titanium dioxide precipitate, and extracted (3 x 10 ml) with methylene chloride. Drying (K_2CO_3) followed by concentration furnished the crude product. Column chromatography on silica gel, eluting with hexane, furnished 83 mg of crystalline 4-methylbiphenyl (59%). mp 47-48°C; ir_{max} 1600, 1485 cm^{-1}; ^{1}H nmr ($CDCl_3$) 2.39 δ (s, 3H, CH_3); mass spectrum *m/e* 168 (p), 167 (p-1), 153 (p-CH_3).[8]

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References and Notes

1. For example see: (a) H. J. J. Loozen, *J. Org. Chem.*, **40**, 520 (1975); (b) S. Danishefsky, C.-F. Yan, R. K. Singh, R. B. Gammill, P. M. McCurry, Jr., N. Fritsch and J. Clardy, *J. Am. Chem. Soc.*, **101**, 7001 (1979); (c) S. Danishefsky, T. Harayama and R. K. Singh, *J. Am. Chem. Soc.*, **101**, 7008 (1979); (d) T.-H. Chan and P. Brownbridge, *Chem. Commun.*, 578 (1979); (e) T.-H. Chan and P. Brownbridge, *J. Am. Chem. Soc.*, **102**, 3534 (1980); (f) N. Takeuchi, K. Ochi, M. Murase and S. Tobinaga, *Chem. Commun.*, 593 (1980); (g) D. L. Boger and M. D. Mullican, *J. Org. Chem.*, **45**, 5002 (1980), and references cited therein.
2. For an excellent synthesis of unsymmetrical biphenyls proceeding from aromatic precursors see: E. C. Taylor, F. Kienzle and A. McKillop, *J. Am. Chem. Soc.*, **92**, 6088 (1970).
3. (a) D. Ayalon-Chass, E. Ehlinger and P. Magnus, *Chem. Commun.*, 772 (1977); (b) Idem., Ibid., 632 (1978); (c) P. W. K. Lau and T.-H. Chan, *Tetrahedron Lett.*, 2383 (1978); (d) E. Ehlinger and P. Magnus, *J. Am. Chem. Soc.*, **102**, 5004 (1980).
4. (a) T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974); (b) T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974); (c) S. Murata, M. Suzuki and R. Noyori, *J. Am. Chem. Soc.*, **102**, 3248 (1980).
5. For the use of silicon in related cationic cyclizations see: (a) W. S. Johnson, T. M. Yarnell, R. F. Myers and D. R. Morton, *Tetrahedron Lett.*, 2549 (1978); (b) T. K. Sarkar and N. H. Andersen, *Tetrahedron Lett.*, 3513 (1978); (c) R. S. Brinkmeyer, *Tetrahedron Lett.*, 207 (1979); (d) A. Itoh, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1783 (1979); (e) I. Kuwajima, T. Tanaka and K. Atsumi, *Chem. Lett.*, 779 (1979); (f) W. S. Johnson, T. M. Yarnell, R. F. Myers, D. R. Morton and S. G. Boots, *J. Org. Chem.*, **45**, 1254 (1980); (g) R. Schmid, P. L. Huesmann and W. S. Johnson, *J. Am. Chem. Soc.*, **102**, 5122 (1980).
6. This reagent is prepared by mixing equimolar quantities of titanium tetrachloride and titanium tetraisopropoxide. T. Mukaiyama, *Ang. Chem., Int. Ed. Engl.*, **16**, 817 (1977).
7. ir_{max} 1600, 1255 cm^{-1}; ^{1}H nmr ($CDCl_3$) 7.13 δ (d, 1H, Ar-H, J = 8.4 Hz), 6.69 δ (m, 2H, Ar-H), 5.75 δ (m, 2H, HC=CH), 3.77 δ (s, 3H, OCH_3), 3.19 δ (br d, 2H, $=C-CH_2-C=$), 0.02 δ (s, 9H, $Si(CH_3)_3$); mass spectrum *m/e* 272 (p), 257 ($p-CH_3$), 199 ($p-Si(CH_3)_3$), 174 ($p-(CH_3)_3SiC{\equiv}CH$), 159 ($p-CH_2CH{=}CHSi(CH_3)_3$), 73 ($Si(CH_3)_3$).
8. The p-1 fragment is prominent in methylbiphenyls: (a) J. L. Laseter, U. Mende and G. W. Griffin, *Org. Mass. Spectrom.*, **4**, 599 (1970); (b) F. Bohlmann, C. Köppel, B. Müller, H. Schwarz and P. Weyerstahl, *Tetrahedron*, **30**, 1011 (1974).

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