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The Use of Conjugated Dienones in Friedel-Crafts Annulations[1]

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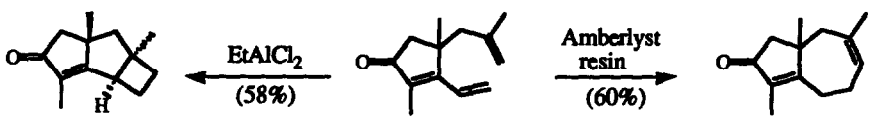
Abstract: Lewis acid-activated conjugated dienones add to electron-rich arenes to create tricyclic compounds containing a central cycloheptane ring.

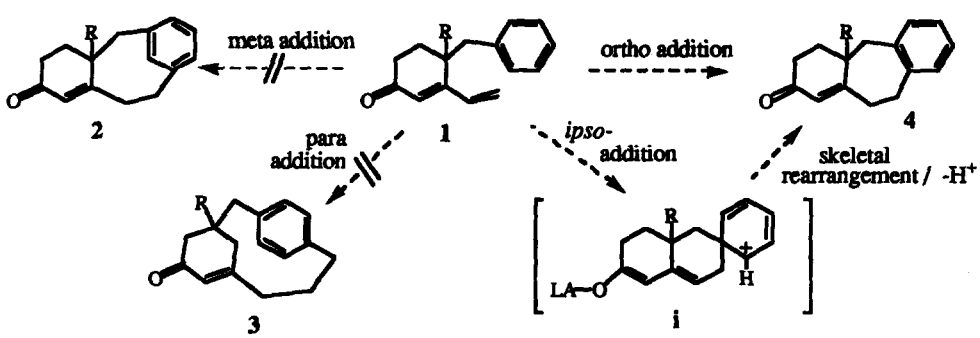
In the cyclization of unactivated alkenes with conjugated 3-vinylcycloalkenones, the use of Lewis acid catalysts produces tricyclic enones containing a fused cyclobutane system, while the use of acidic Amberlyst resins results in the annulation of a cycloheptane ring (Equation 1).[3]

Equation 1



We were curious whether Lewis acid-activated conjugated dienones could be used in cyclialkylations.[4] Although electrophilic substitution could potentially occur at three sites (Scheme 1), the geometric constraints imposed by the intramolecular nature of the reaction makes the formation of enones 2 and 3 unlikely. Enone 4, however, could result from either addition at an ortho position or from *ipso*-attack, followed by an acid-promoted rearrangement and re-aromatization. These uncertainties motivated us to investigate this annulation strategy.

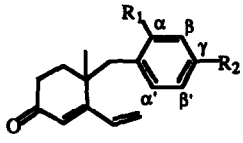
Scheme 1



Arene-dienones **5** and **8** were prepared in hopes that the inductive effect of the benzylic methylene would activate the aromatic ring towards substitution.[5] These simple substrates, however, failed to react despite a wide variety of Lewis acids and reaction conditions (Equation 2).

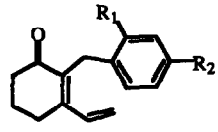
We next prepared substrates containing a second electron donating group to increase the reactivity of the arene. An electron donating group positioned β to the carbon bearing the benzylic methylene would activate the arene towards substitution at either the α or α' positions, while an electron donating group positioned at the α or γ sites would activate the β or β' positions which are too remote to react with the electrophilic species.[6] Indeed, substrates **6**, **7**, **9** and **10** either failed to cyclize or produced adducts resulting from 1,6-addition of chloride ion when chlorinated Lewis acids were used.[7]

Equation 2



4-arene-dienone series

$R_1 = R_2 = H$ **(5)**
$R_1 = OCH_3$, $R_2 = H$ **(6)**
$R_1 = H$, $R_2 = OCH_3$ **(7)**

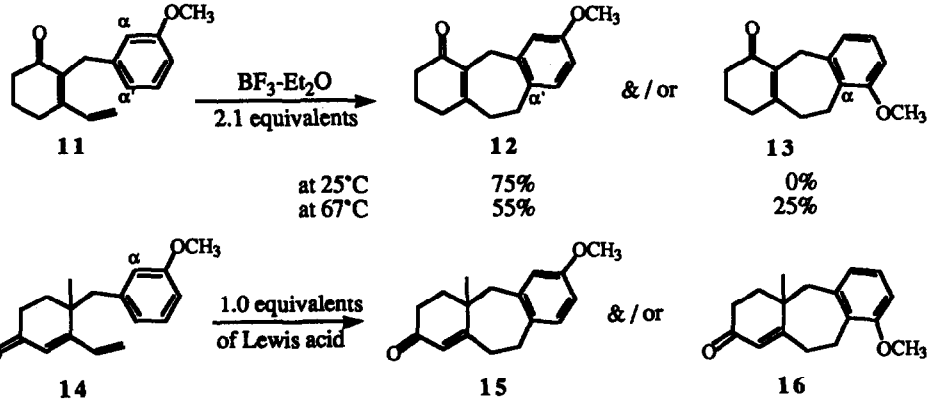


2-arene-dienone series

$R_1 = R_2 = H$ **(8)**
$R_1 = OCH_3$, $R_2 = H$ **(9)**
$R_1 = H$, $R_2 = OCH_3$ **(10)**

The viability of this annulation strategy was demonstrated when arene-dienones **11** and **14** cyclized to give products corresponding to both ortho and para addition. At room temperature the steric and inductive effects of the methoxy group combine to deactivate the ortho position (α), and lead to the formation of only enone **12** through α' addition. However, at elevated temperatures enone **13**, which results from ortho substitution, was isolated in low yield. Note that 2-arene-dienone **11** required more Lewis acid to promote cyclization than did 4-arene-dienone **14**. This trend is more pronounced in upcoming examples.

Chart 1



11 → **12** + **13**

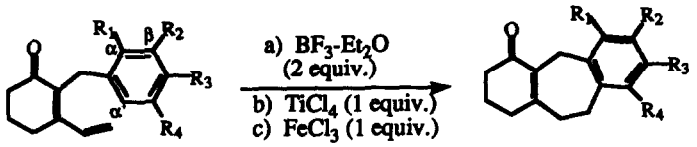
	12	**13**
at 25°C	75%	0%
at 67°C	55%	25%

14 → **15** + **16**

	15	**16**
BF_3-Et_2O (25°C)	75%	11%
$TiCl_4$	73%	0%
$FeCl_3$	70%	11%

Cyclization is quite facile when the arene ring contains three activating groups (Charts 2 and 3). In the case of dimethoxy ethers **21** and **29**, the strongly activating methoxy groups are positioned so that their directive influence reinforces each other. Not surprisingly, these substrates cyclize easily and in high

Chart 2



$R_1 = R_2 = OCH_3$, $R_3 = R_4 = H$ **(17)** — Using "a" at 25°C (82%) **(18)**

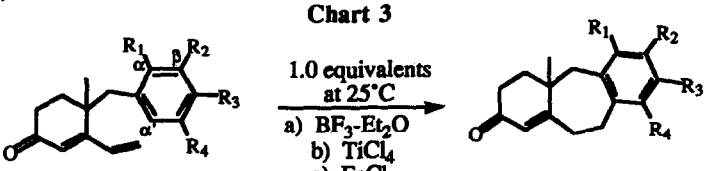
$R_1 = H$, $R_2 = R_3 = OCH_3$, $R_4 = H$ **(19)** — Using "a" at 25°C (0%) **(20)**; "a" at 67°C (77%)

$R_1 = R_3 = H$, $R_2 = R_4 = OCH_3$ **(21)** — Using "a" at 25°C (97%) **(22)**; "b" at 25°C (63%); "c" at 25°C (38%)

$R_1 = OCH_3$, $R_2 = R_3 = H$, $R_4 = OCH_3$ **(23)** — Using "a" at 25°C (5%) **(24)** / **23** (95%); "a" at 67°C (92%); "c" at 25°C (67%)

yield, independent of the catalyst used. Other electron rich substrates, such as **19** and **27**, undergo substitution at the sterically less congested site (α' vs α) relative to the β-methoxy group. We observed that ferric chloride-promoted cyclization and demethylation of the ethers resulted in lower yields of the cyclized products.

Chart 3



$R_1 = R_2 = OCH_3$, $R_3 = R_4 = H$ **(25)** — Using "a" (99%) **(26)**; "b" (73%); "c" (80%)

$R_1 = H$, $R_2 = R_3 = OCH_3$, $R_4 = H$ **(27)** — Using "a" (81%) **(28)**; "b" (74%); "c" (81%)

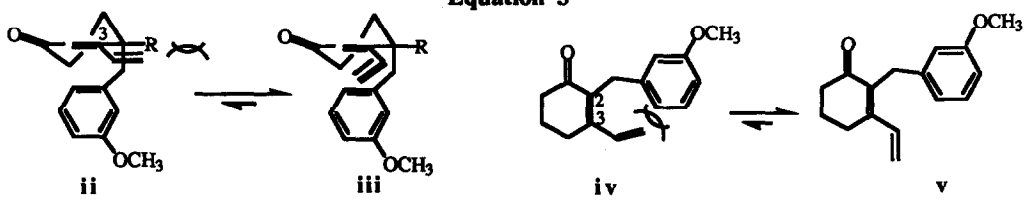
$R_1 = R_3 = H$, $R_2 = R_4 = OCH_3$ **(29)** — Using "a" (95%) **(30)**; "b" (62%); "c" (76%)

$R_1 = OCH_3$, $R_2 = R_3 = H$, $R_4 = OCH_3$ **(31)** — Using "a" (61%) **(32)**; "b" (85%); "c" (72%)

4-Arene-dienones are more reactive than 2-arene-dienones because of conformation considerations. In the 4-arene-dienone series steric interactions between the C(3) vinyl group and the equatorially oriented alkyl group favor the cisoid dienone conformation (cf. ii → iii, Equation 3), wherein both the para and ortho positions of the arene ring are accessible. In the 2-arene-dienone series, steric interactions between the C(2) and C(3) substituents in conformation iv cause the transoid conformer (v) to dominate, thereby

precluding cyclization. This unfavorable equilibrium slows the reaction rate and is only overcome by using more vigorous conditions.[8]

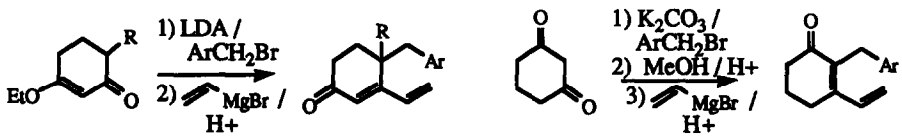
Equation 3



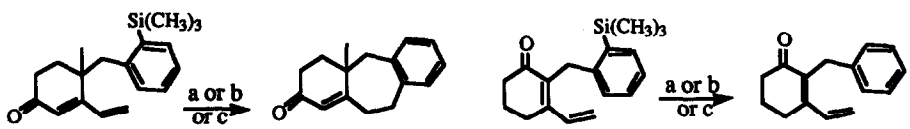
In summary, intramolecular Friedel-Crafts ring closures occur when the arene ring is functionalized with several activating groups. Although these annulations are governed by the directing nature of the activating groups, the site of substitution is strongly influenced by geometric constraints. In this study, we observed that 4-arene-dienones cyclize far more readily than comparably functionalized 2-arene-dienones. Although skeletal rearrangements are common in Friedel-Crafts reactions, products corresponding to such rearrangements were not observed. This suggests that these annulations do not proceed by means of an *ipso*-attack-based mechanism. Finally, this methodology has permitted a short synthesis of the diterpene barbatusol.[9] Other synthetic applications are forthcoming.

REFERENCES AND NOTES:

1. Taken in part from the MS thesis of Mr. T. Lee Feltman, *The University of Georgia* (1992).
2. PRF Summer Undergraduate Research Recipient (1992).
3. Majetich, G.; Khetani, V. Tetrahedron Lett. **1990**, *31*, 2243.
4. The term "cyclialkylations" was first used by Bruson and Kroeger to describe all electrophilic ring closures on to aromatic systems. See: a) Barclay, L. R. *Cyclialkylaton of Aromatics* in Olah, G. A. "Friedel-Crafts and Related Reactions," Vol. II; Wiley-Interscience: New York, 1964, pp 785-977. b) Olah, G. A. "Friedel-Crafts Chemistry", Wiley: New York, **1973**.
5. The preparation of requisite substrates is generalized below:



6. We have also studied substrates substituted with a trimethylsilyl group. While cyclization occurs in the more reactive 4-arene-dienone example, the silyl moiety is lost in both cases.



a = BF_3-Et_2O (65%); b = $TiCl_4$ (56%); c = $FeCl_3$ (30%)

a = BF_3-Et_2O; b = $TiCl_4$; c = $FeCl_3$

7. The δ-chloro-cyclohexenone byproducts failed to cyclize upon reaction with other Lewis acids.
8. For a more detailed conformational analysis in the context of intramolecular allylsilane additions to conjugated dienones, see: Majetich, G.; Defauw, J.; Ringold, C. R. J. Org. Chem. **1988**, *53*, 50.
9. Majetich, G.; Zhang, Y.; Feltman, T. L.; Duncan, S., Jr., "The Total Synthesis of (±)-Barbatusol," the next Letter.

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