

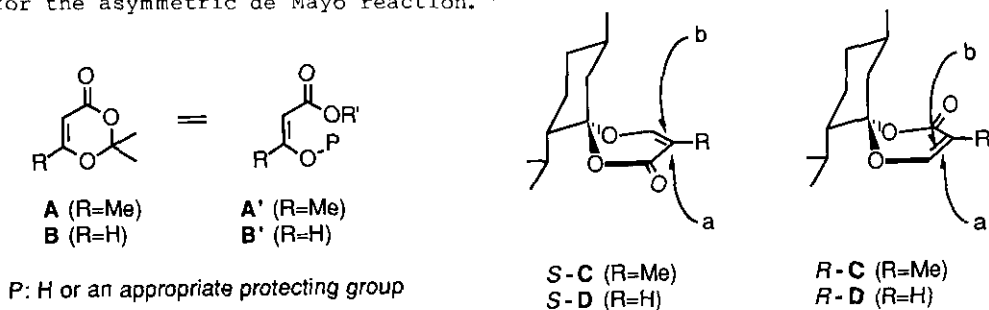
REGIO- AND STEREOCONTROLS IN THE PHOTO[2+2]CYCLOADDITION OF
1,3-DIOXIN-4-ONES TO ALKENES. USE OF AN ESTER GROUP AS THE
CONNECTING UNIT IN THE INTRAMOLECULAR VARIANT^{1,2}

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Abstract---Intramolecular photo[2+2]cycloaddition of dioxinones to alkene to give eight membered lactones proceeds with complete stereo- and high regioselectivities when an ester group presents as a linking unit between the acetal carbon and the double bond of the side chain. The successful separation of some dioxinones into the enantiomers indicates the method is useful for synthesis of enantiomerically pure compounds.

The [2+2]cycloaddition of enones and enone-like chromophores to olefins is by far the most widely employed photochemical reaction in organic synthesis.³ One demerit of the method is low regio- and stereoselectivities inherent to the intermolecular reactions. In the intramolecular variant of the reaction,⁴ the problems inherent to the regio- and stereoselectivities are substantially reduced owing to obvious geometrical constraints imposed on the reaction sites. Recent use of dioxinones (A and B) as the alternatives for acetoacetates and formylacetates (A' and B': both of which are incapable of photoaddition to olefins) has further broadened the scope of the de Mayo reaction.⁵ The use of the rigid spirocyclic dioxinones (C and D),⁶ whose a-side is more exposed than b-side as the chiral enones, permits ready access of diastereoisomeric, and ultimately enantiomeric products, and hence, provides novel and effective method for the asymmetric de Mayo reaction.^{7,8}



Scheme 1

In order to broaden this methodology further, it is necessary to know to what extent one can attain regio- as well as stereoselectivities in the photoadditions. At first, we examined the intermolecular photoaddition of the dioxinone to olefins and then extended it to the intramolecular valiant. As a result, we have explored an efficient method for the construction of all cis-1,2,3-trisubstituted cyclobutanes.

Photoadditions⁹ of the dioxinone (1) to four olefins (2-5) were examined at first. The result summarized in Table 1 shows that exclusive formation of the head-to-tail (H-T) adducts (7)¹⁰ was realized only in case of electron-rich olefins (3-5). Also, though exo-adducts were obtained as the major products, significant formation of endo-adducts was observed irrespective of the mono-substituted olefins (2-4). Thus, complete regio- and stereocontrol was accomplished only by using ketene diethylacetal (5). Though the use of propargyl acetate (6) as the olefin afforded all cis-cyclobutane (7-endo; X = CH₂OAc) via catalytic hydrogenation of the H-T adduct (7'), the method is still unsatisfactory due to formation of the H-H adduct (8') as in the case of 2.

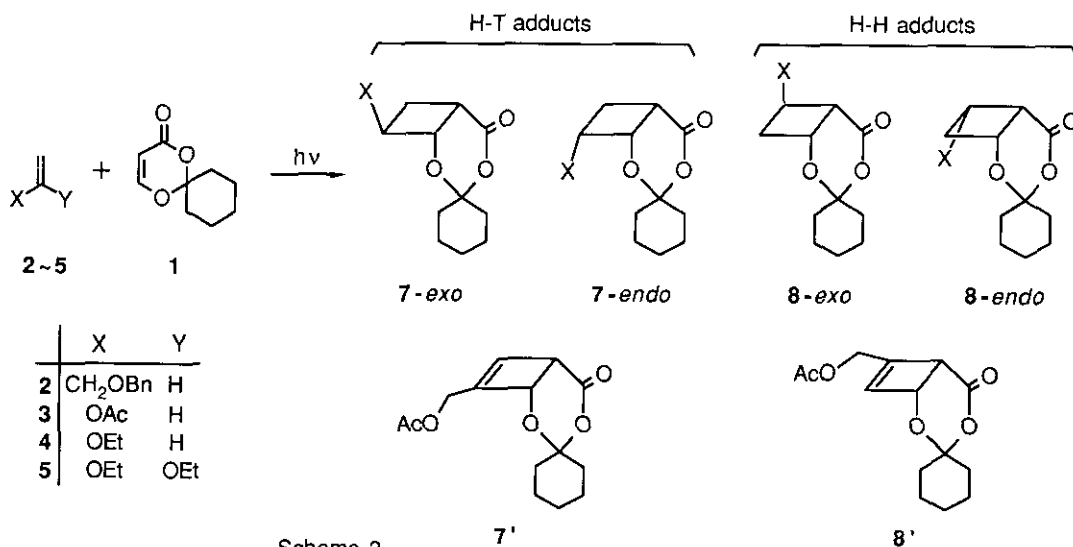
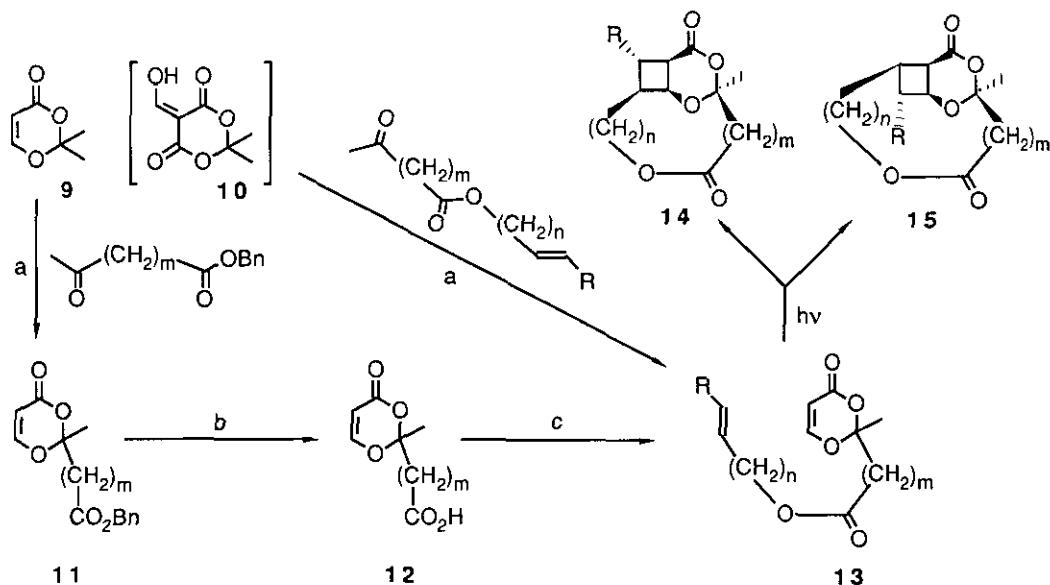


Table 1. Photoproducts derived from 1 and olefins (2-6)

Olefin	X	Y	H-T adduct (%)		H-H adduct (%)	
			7- <u>exo</u>	7- <u>endo</u>	8- <u>exo</u>	8- <u>endo</u>
2	CH ₂ OBn	H	28	14	20	5
3	OAc	H	26	28	0	0
4	OEt	H	37	8	0	0
5	OEt	OEt		71		0
6	CH≡CCH ₂ OAc		35			16

In order to realize regio- and stereoselective route to 1,2,3-trisubstituted cyclobutanes irrespective of the kind of olefins, we then examined the strategy using intramolecular photo[2+2]cycloaddition of dioxinones whose acetal carbon is connected with an appropriate olefin by an ester group (Scheme 3). The merits are: 1) both acetal and ester groups in the photoadduct can be cleaved readily, 2) by choosing m and n , one can attain the adducts with high selectivity formally identical with the ones derived from intermolecular addition reactions using the corresponding olefins, and 3) resolution of racemic dioxinones (e.g. 13), if realized, would provide the corresponding adduct in enantiomerically pure compounds (EPC). According to this strategy, two synthetic routes (methods A and B) to the dioxinones (13) from either the 2,2-dimethyl derivative (9) or formylated Meldrum's acid (10) were elaborated by an application of our general method (Scheme 3).^{6,11} Thus, just heating of 9 or 10 in the presence of an appropriate alkenol ester of keto acid afforded 13 in a satisfactory yield (method A). Alternatively, the benzyl ester (11) obtained in a similar manner was converted to the carboxylic acid (12), which was condensed with an alkenol by DCC method to give 13 (method B).¹²

Resolution of 11 ($m=0$, mp 48-49 °C) by hplc with ChiraSpher (Merck) afforded readily each enantiomer [mp 68-68.5 °C, $[\alpha]_D^{25} +77.8^\circ$ or -77.1° (CHCl_3)] as EPC and, hence, following result using racemic series seems to be extendable to EPC synthesis. The result of photoreaction of these dioxinones (13) is listed in Table 2.¹³



Scheme 3. Reagents and conditions. a: reflux in toluene in the presence of a keto ester; b: H_2 / Pd-C / AcOEt ; c: ester formation with an alkenol by DCC method.

Table 2. Intramolecular photoaddition of 13 to give the lactones (14 and 15)

	Dioxinone (13)			Yield of	Parallel Adduct (14)	Cross Adduct (15)	Ratio (14/15)
	R	m	n	Adduct (%)	Isolated Yield (%)	Isolated Yield (%)	
a	H	0	1	-- ^{a)}	-- ^{a)}	-- ^{a)}	--
b	H	0	2	65	60	5	10
c	H	0	3	70	35 ^{b)}	35 ^{b)}	1 ^{b)}
d	H	0	9		0 ^{c)}	0 ^{c)}	--
e	H	2	0	91	91	0	>100
f	H	2	1	95	80	15	5.3
g	Me	2	1	82	70	12	5.8

a) None of isolable products was obtained.

b) Separation of isomers was unsuccessful. The ratio was determined by ¹H-nmr.

c) Only dimers formed at the enone part of the dioxinone were obtained.

It is evident that in both series (m = 0 or 2) of compounds, parallel adducts (14) are formed predominantly (parallel/cross = 10 for 13b and >100 for 13e) only if m+n = 2. In the dioxinones with m = 2, the high parallel/cross ratio (5.3 for 13f) is observed even when m+n = 3. It is worthy to mention that single parallel adduct was formed from 13g. Though experimental verification is not yet done, it seems reasonable that the fourth substituent (R) on the adduct should take exo configuration irrespective of the configuration of the C=C bond in the starting dioxinones [note that the transition state giving all cis adduct seems improbable due to steric crowding].

The present method for the construction of all cis-1,2,3-trisubstituted cyclobutanes satisfies all of the afore-mentioned requirements (1-3). In connection with the [2+2]photocycloaddition using dioxinones, we have already demonstrated that i) much different from the spirocyclic dioxinones (e.g. D), monocyclic dioxinones having a chiral acetal carbon shows poor face selectivity in the intermolecular photoaddition¹⁴ (hence can not be used for EPC synthesis) and ii) though the spirocyclic dioxinones having ω-alkenyl side chain on the C=C bond shows high face selectivity,¹⁵ the chain is unremovable. Hence, elongation of side chain from the acetal center with an appropriate removable connecting unit¹⁶ as presented in this paper would provide new and effective methodology for the one aiming to construct complex molecules as EPC by the use of dioxinones as the key intermediates.

ACKNOWLEDGMENT

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