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Polarity Inversion of Donor−Acceptor Cyclopropanes: Disubstituted δ-Lactones via Enantioselective Iridium Catalysis

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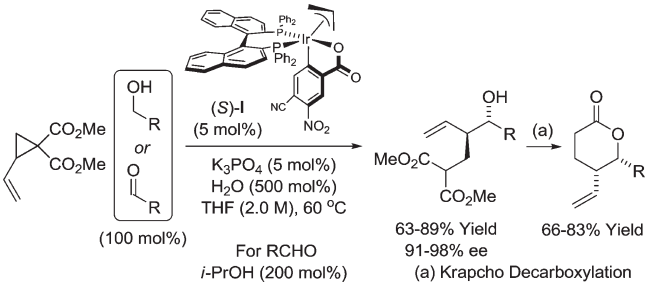
Supporting Information

ABSTRACT: The coupling of carbonyl electrophiles at the donor position of donor−acceptor cyclopropanes is described, representing an inversion of polarity with respect to conventional reactivity modes displayed by these reagents. Specifically, upon exposure of donor−acceptor cyclopropanes to alcohols in the presence of a cyclometalated iridium catalyst modified by (*S*)-BINAP, catalytic C−C coupling occurs, providing enantiomerically enriched products of carbonyl allylation. Identical products are obtained upon isopropanol-mediated transfer hydrogenation of donor−acceptor cyclopropanes in the presence of aldehydes. The reaction products are directly transformed to *cis*-4,5-disubstituted δ-lactones.

Cyclopropanes are useful synthetic building blocks for organic synthesis because of their multifaceted reactivity and relative ease of preparation.[1] Donor−acceptor (D−A) cyclopropanes are a particularly useful subset capable of reacting with diverse partners upon exposure to the proper kinetic trigger.[2] All polar reactions of D−A cyclopropanes involve nucleophilic trapping at the donor site and electrophilic trapping at the acceptor site, as illustrated in the stereoselective syntheses of five- and six-membered ring products (Figure 1a,b).[3] Although inversion (or *umpolung*) of these polarity patterns would increase the diversity of products accessible from D−A cyclopropanes, such reactivity remains elusive (Figure 1a,d).[4] Here we report that exposure of D−A cyclopropanes to cyclometalated iridium catalysts results in umpolung of the D−A cyclopropanes, leading to electrophilic trapping at the donor site, as illustrated by the enantioselective C−C coupling of D−A cyclopropanes and carbonyl electrophiles to furnish δ-lactones.



The reaction of D−A cyclopropanes with transition metals to form *electrophilic* π-allyl intermediates is an established mode of reactivity used to prepare carbo- and heterocyclic products (Figure 1c).[5] While the generation of *nucleophilic* π-allyls from D−A cyclopropanes is unknown (Figure 1d),[4] the feasibility of umpoled carbonyl additions involving D−A cyclopropanes is suggested by recently developed reductive couplings of allylic carboxylates to carbonyl partners catalyzed by *ortho*-cyclometalated iridium *C,O*-benzoates.[6,7] A unique feature of such iridium-catalyzed carbonyl allylations resides in the use of alcohols as terminal reductants, allowing highly enantioselective carbonyl addition from the alcohol or aldehyde oxidation level in the absence of stoichiometric metallic reagents. Although similar capabilities may be envisioned for corresponding D−A cyclopropane-mediated processes, π-allyl generation requires a malonic ester moiety to function as an efficient nucleofuge for oxidative addition,[7] which at the onset of these studies had not been demonstrated for iridium.

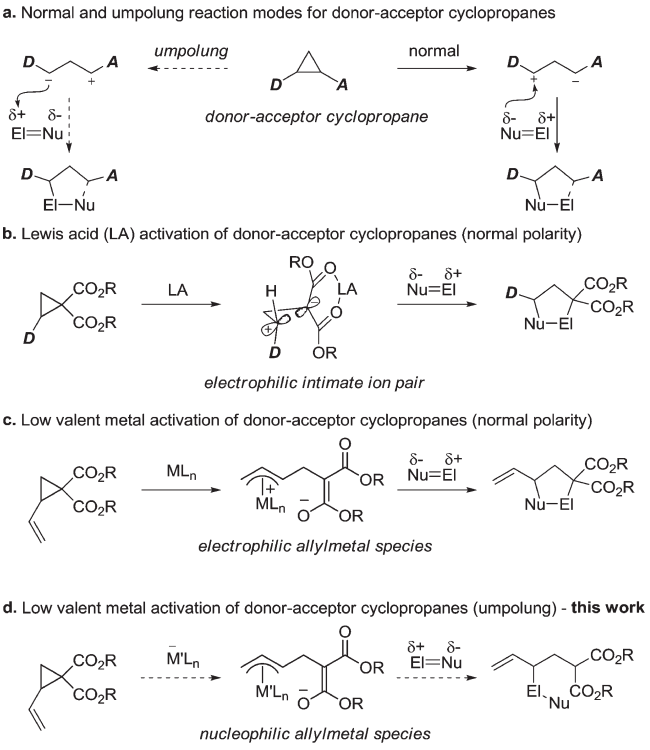


Figure 1. Lewis acid and transition metal activation of D−A cyclopropanes.

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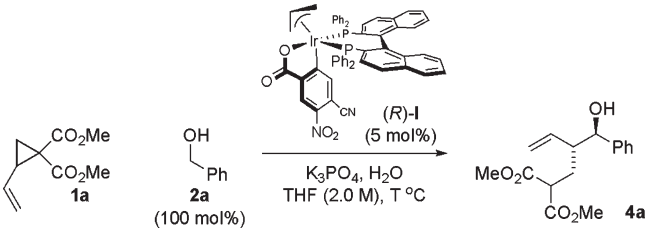
Table 1. Optimization of D−A Cyclopropane-Mediated Carbonyl Allylation of Benzyl Alcohol (2a)[a]



entry	K_3PO_4 mol %	H_2O mol %	temp (°C)	**1a** mol %	% yield	% ee (dr)
1	50	500	50	200	37	99 (>20:1)
2	0	500	50	200	0	N/A
3	5	500	50	200	81	98 (8:1)
4	5	0	50	200	0	N/A
5	5	500	60	200	84	98 (7:1)
6	5	500	60	150	84	98 (6:1)

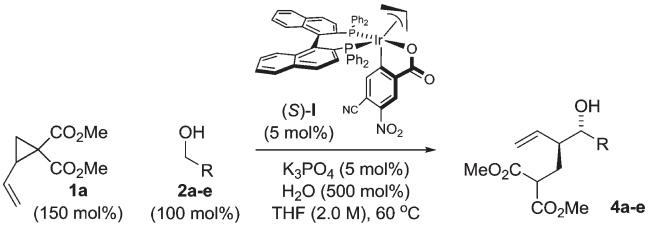
[a] Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral-stationary-phase HPLC analysis. See the Supporting Information for further details.

Further, as reported by one of the present authors,[5d] under the conditions of palladium catalysis, D−A cyclopropanes and aldehydes combine by way of π-allyl intermediates to form tetrahydrofurans (conceptualized in Figure 1c). Thus, the proposed umpoled process must compete with an efficient π-allyl-mediated transformation involving identical reactants, rendering the outcome of this endeavor uncertain.

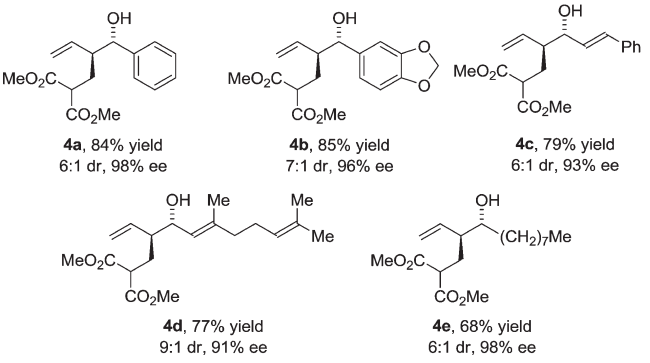
Vinylcyclopropane **1a** was prepared directly from the commercial reagents dimethyl malonate and (*E*)-1,4-dibromobut-2-ene.[5d] In preliminary experiments, **1a** (200 mol %) and benzyl alcohol (**2a**; 100 mol %) were exposed to the chromatographically isolated π-allyliridium complex (*R*)-**I** (5 mol %) at 50 °C under conditions effective for related crotylations employing α-methylallyl acetate.[7d] Gratifyingly, the desired adduct **4a** formed as a single regioisomer with nearly complete levels of diastereo- and enantioselectivity, although the isolated yield was modest (Table 1, entry 1). The diastereoselectivity observed in the formation of **4a** was amplified by competing base-catalyzed lactonization arising predominantly from the minor diastereomer. As all atoms in vinylcyclopropane **1a** and alcohol **2a** appear in the product, it was postulated that exogenous base may be unnecessary and in fact may impede the reaction. While upon omission of K_3PO_4 adduct **4a** was not formed (entry 2), a decreased loading of K_3PO_4 (5 mol %) dramatically improved the isolated yield of **4a** (entry 3). Upon a slight increase in temperature (entries 5 and 6) and decrease in the loading of vinylcyclopropane **1** (entry 6), adduct **4a** was produced in 84% isolated yield with good levels of diastereoselectivity and excellent levels of enantioselectivity.

These latter conditions were applied to benzylic alcohols **2a** and **3a**, allylic alcohols **2c** and **2d**, and aliphatic alcohol **2e**. Good isolated yields of the corresponding adducts **4a**−**e** were observed, and in each case, good levels of diastereoselectivity were accompanied by exceptional levels of enantiocontrol (Table 2). As observed in prior studies,[6,7] an identical set of adducts **4a**−**e** are accessible from the aldehyde oxidation level

Table 2. D−A Cyclopropane-Mediated Carbonyl Allylation from the Alcohol Oxidation Level[a]

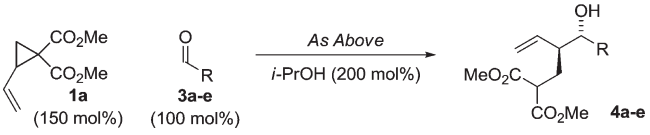


2a, R = Ph; **2b**, R = piperonyl; **2c**, R = (*E*)-CH=CH$_2$Ph; **2d**, R = geranyl; **2e**, R = *n*-octyl

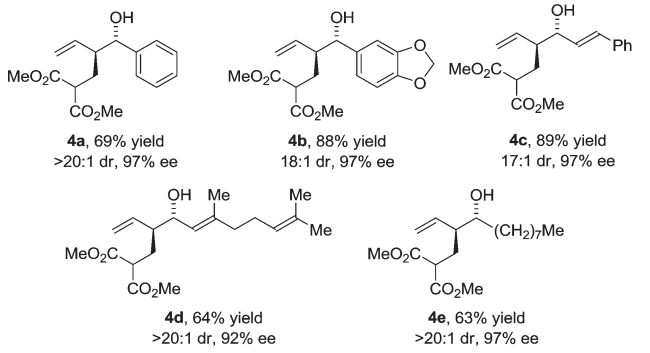


[a] As described for Table 1.

Table 3. D−A Cyclopropane-Mediated Carbonyl Allylation from the Aldehyde Oxidation Level[a]



3a, R = Ph; **3b**, R = piperonyl; **3c**, R = (*E*)-CH=CH$_2$Ph; **3d**, R = geranyl; **3e**, R = *n*-octyl



[a] As described for Table 1.

upon use of *i*-PrOH (200 mol %) as the terminal reductant under otherwise identical reaction conditions. Again, good isolated yields and diastereo- and enantioselectivities were observed (Table 3). Thus, umpoled D−A cyclopropane-mediated carbonyl allylation occurs with equal facility from the alcohol or aldehyde oxidation level (Tables 2 and 3). The absolute stereochemical assignment of adducts **4a**−**e** was

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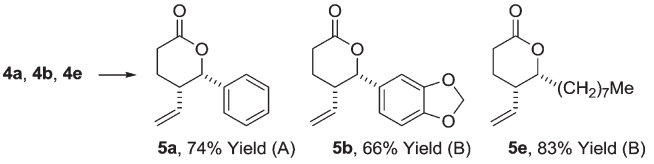
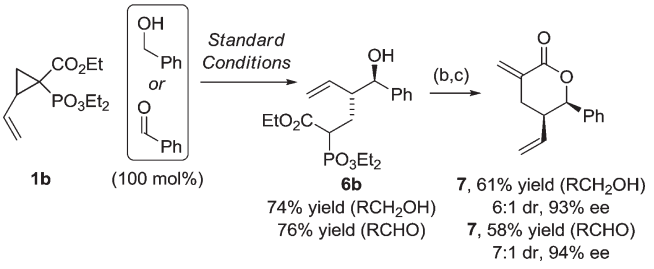
Scheme 1. Formation of *cis*-4,5-Disubstituted δ-Lactones 5a, 5b, and 5e via Krapcho Decarboxylation[a]



[a] Conditions A: LiCl (500 mol %), 3 Å molecular sieves, DMSO (1 M), 150 °C. Conditions B: NaCl (500 mol %), DMSO (0.2 M), 160 °C.

Scheme 2. Reactions of D−A Cyclopropane 1b Incorporating a Phosphonoacetate Moiety[a]



[a] Reagents: (a) Standard conditions as described in Table 1 using catalyst (*R*)-**I**. (b) K_2CO_3, CH_2O, H_2O, 60 °C. (c) DCC, DMAP, CH_2Cl_2, 23 °C.

made on the basis of single-crystal X-ray diffraction analysis, as described in the Supporting Information.

To explore the utility of the coupling products, adducts **4a**, **4b**, and **4e** were subjected to conditions for Krapcho decarboxylation, resulting in the formation of *cis*-4,5-disubstituted δ-lactones **5a**, **5b**, and **5e**, respectively. Notably, lactones of this type appear as substructures in natural products such as leustroducsin[8] and phoslactomycin[9] (Scheme 1). The range of compounds availed through this approach was further expanded through variation of the acceptor group, as in D−A cyclopropane **1b**, which incorporates a phosphonoacetate moiety. **1b** reacts with benzyl alcohol and benzaldehyde under the standard conditions to provide adduct **6b**. The methine adjacent to the acceptor group in adduct **6b** represents a third, undefined stereogenic center, requiring evaluation of the diastereo- and enantioselectivity at a subsequent stage. For compound **6b**, the Horner−Wadsworth−Emmons reaction with paraformaldehyde occurred with concomitant saponification to provide the methylidene carboxylic acid, which upon exposure to dicyclohexylcarbodiimide (DCC) was transformed to the α-methylene glutarolactone **7**. The enantiomeric excess was determined at this stage (Scheme 2).

In summary, we report umpoled reactions of donor−acceptor cyclopropanes, as illustrated by diastereo- and enantioselective iridium-catalyzed D−A cyclopropane-mediated carbonyl allylations from the alcohol or aldehyde oxidation levels. These studies open new routes to optically enriched *cis*-4,5-disubstituted δ-lactones. Of broader significance, identification of the structural and interactional features of the catalytic system required for polarity inversion provide a foundation for the development of related C−C coupling processes.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures; spectral and HPLC data; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The version published ASAP October 31, 2011, did not contain the final corrections in the text and the first graphic. The corrected version was reposted November 16, 2011.