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

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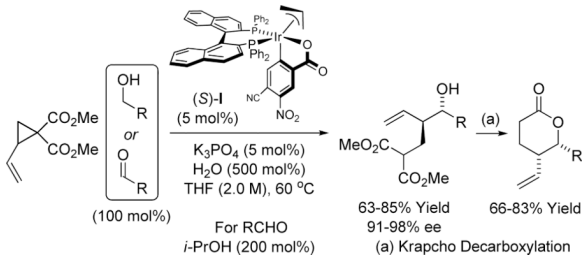
Abstract

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 cyclometallated iridium catalyst modified by (*S*)-BINAP, catalytic C-C coupling occurs to provide 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 due to 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 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 donor-acceptor cyclopropanes to cyclometallated iridium catalysts results in the *umpolung* of D-A cyclopropanes, resulting in 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.



This paper is dedicated to Professors D. A. Evans and B. M. Trost on the occasion of their 70th birthdays.

Supporting Information Available: Experimental procedures, spectral, HPLC and GC data. This material is available free of charge *via* the internet at http://pubs.acs.org.

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*-cyclometallated 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. 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** is prepared directly from the commercial reagents dimethyl malonate and (*E*)-1,4-dibromobut-2-ene.[5d] In preliminary experiments, vinylcyclopropane **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-methyl allyl 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** is 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 reaction. While upon omission of K_3PO_4 adduct **4a** is not formed (Table 1, entry 2), a decreased loading of K_3PO_4 (5 mol%) dramatically improved the isolated yield of **4a** (Table 1, entry 3). Upon a slight increase in temperature (Table 1, entry 5) and decrease in the loading of vinylcyclopropane **1**, adduct **4a** was produced in 84% isolated yield with good levels of diastereoselectivity and excellent levels of enantioselectivity (Table 1, entry 6).

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–4e** 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–4e** are accessible from the aldehyde oxidation level upon use of *i*-PrOH (200 mol %) as the terminal reductant under otherwise identical reaction conditions. Again, good isolated yields, 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–4e** is 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 formation of *cis*-4,5-disubstituted δ-lactones **5a, 5b** and **5e**. 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 is expanded further through variation of the acceptor group, as

in D-A cyclopropanes **1b**, which incorporates a phosphonoacetate moiety. D-A cyclopropanes **1b** reacts with either benzyl alcohol or benzaldehyde under standard conditions to provide adducts **6b** and **6c**, respectively. The methine adjacent to the acceptor groups of adducts **6b** and **6c** represents a third, undefined stereogenic center, requiring evaluation of diastereo- and enantioselectivity at a subsequent stage. For compound **6b**, Horner-Wadsworth-Emmons reaction with paraformaldehyde occurs with concomitant saponification to provide the methylidene carboxylic acid, which upon exposure to dicyclohexylcarbodiimide (DCC) is transformed to the α-methylene glutarolactone **7**. Enantiomeric excess was determined at this stage (Scheme 2).

In summary, we report the first umpoled reactions of D-A 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

1. For a review on the stereoselective synthesis of substituted cyclopropanes, see: Lebel H, Marcoux J-F, Molinaro C, Charette AB. Chem. Rev. 2003; 103:977. [PubMed: 12683775]
2. For D-A cyclopropane reviews, see: (a) Reissig H-U, Zimmer R. Chem. Rev. 2003; 103:1151. [PubMed: 12683780] (b) Yu M, Pagenkopf BL. Tetrahedron. 2005; 61:321. (c) Rubin M, Rubina M, Gevorgyan V. Chem. Rev. 2007; 107:3117. [PubMed: 17622181] (d) Carson CA, Kerr MA. Chem. Soc. Rev. 2009; 38:3051. [PubMed: 19847340] (e) De Simone F, Waser J. Synthesis. 2009:3353. (f) Campbell MJ, Johnson JS, Parsons AT, Pohlhaus PD, Sanders SD. J. Org. Chem. 2010; 75:6317. [PubMed: 20863142]
3. For selected examples in synthesis, see: Sugita Y, Kawai K, Yokoe I. Heterocycles. 2000; 53:657. (b) Lautens M, Han W. J. Am. Chem.Soc. 2002; 124:6312. [PubMed: 12033859] (c) Young IS, Kerr MA. Angew. Chem. Int. Ed. 2003; 42:3023. (d) Pohlhaus PD, Johnson JS. J. Org. Chem. 2005; 70:1057. [PubMed: 15675870] (e) Carson CA, Kerr MA. J. Org. Chem. 2005; 70:8242. [PubMed: 16277360] (f) Kang Y-B, Tang Y, Sun X-L. Org. Biomol. Chem. 2006; 4:299. [PubMed: 16391772] (g) Korotkov VS, Larionov OV, Hofmeister A, Magull J, de Meijere A. J. Org. Chem. 2007; 72:7504. [PubMed: 17824644] (h) Bajtos B, Yu M, Zhao H, Pagenkopf BL. J. Am. Chem. Soc. 2007; 129:9631. [PubMed: 17630734] (i) Perreault C, Goudreau SR, Zimmer LE, Charette AB. Org. Lett. 2008; 10:689. [PubMed: 18257580] (j) Lebold TP, Leduc AB, Kerr MA. Org. Lett. 2009; 11:3770. [PubMed: 19719208] (k) Parsons AT, Johnson JS. J. Am. Chem. Soc. 2009; 131:14202. [PubMed: 19764759] (l) Parsons AT, Smith AG, Neel AN, Johnson JS. J. Am. Chem. Soc. 2010; 132:9688. [PubMed: 20572661] (m) Smith AG, Slade MC, Johnson JS. Org. Lett. 2011; 13:1996. [PubMed: 21395241]
4. For examples of nucleophilic allylation of aldehydes and acetals at vinyl cylopropane donor sites *via in-situ* borylation, see: (a) Sumida Y, Yorimitsu H, Oshima K. Org. Lett. 2008; 10:4677. [PubMed: 18808132] (b) Selander N, Szabo KJ. Chem, Comm. 2008:3420. [PubMed: 18633509]
5. (a) Shimizu I, Ohashi Y, Tsuji J. Tetrahedron Lett. 1985; 26:3825.(b) Yamamoto K, Ishida T, Tsuji J. Chem. Lett. 1987; 6:1157.(c) Bowman RK, Johnson JS. Org. Lett. 2006; 8:573. [PubMed:

16468714] (d) Parsons AT, Campbell MJ, Johnson JS. Org. Lett. 2008; 10:2541. [PubMed: 18503280] (e) Trost BM, Morris PJ. Angew. Chem. Int. Ed. 2011; 50:6167.(f) Goldberg AFG, Stoltz BM. Org. Lett. 2011; 13:4474–4476. [PubMed: 21786746]

6. For a review, see: Bower JF, Krische MJ. Top. Organomet. Chem. 2011; 43:107. [PubMed: 21822399]
7. For selected examples of enantioselective carbonyl allylation by iridium catalyzed C-C bond-forming transfer hydrogenation, see: (a) Kim IS, Ngai M-Y, Krische MJ. J. Am. Chem. Soc. 2008; 130:6340. [PubMed: 18444616] (b) Kim IS, Ngai M-Y, Krische MJ. J. Am. Chem. Soc. 2008; 130:14891. [PubMed: 18841896] (c) Kim IS, Han SB, Krische MJ. J. Am. Chem. Soc. 2009; 131:2514. [PubMed: 19191498] (d) Gao X, Townsend IA, Krische MJ. J. Org. Chem. 2011; 76:2350. [PubMed: 21375283] (e) Han SB, Kim IS, Han H, Krische MJ. J. Am. Chem. Soc. 2009; 131:6916. [PubMed: 19453190] (f) Lu Y, Kim IS, Hassan A, Del Valle DJ, Krische MJ. Angew. Chem. Int. Ed. 2009; 48:5018.
8. (a) Kohama T, Enokita R, Okazaki T, Miyaoka H, Torikata A, Inukai M, Kaneko I, Kagasaki T, Sakaida Y, Satoh A, Shirashi A. J. Antibiot. 1993; 46:1503. [PubMed: 7503975] (b) Kohama T, Nakamura T, Kinoshita T, Kaneko I, Shiraishi A. J. Antibiot. 1993; 46:1512. [PubMed: 7503976] (c) Matsuhashi H, Shimada K. Tetrahedron. 2002; 58:5619.
9. (a) Fushimi S, Nishikawa S, Shimazo A, Seto H. J. Antibiot. 1989; 42:1019. [PubMed: 2753808] (b) Fushimi S, Furihata K, Seto H. J. Antibiot. 1989; 42:1026. [PubMed: 2753809] (c) Ozasa T, Suzuki K, Sasamata M, Tanaka K, Koburi M, Kadota S, Nagai K, Saito T, Watanabe S, Iwanami M. J. Antibiot. 1989; 42:1331. [PubMed: 2793586] (d) Ozasa T, Tanaka K, Sasamata M, Kaniwa H, Shimizu M, Matsumoto H, Iwanami M. J. Antibiot. 1989; 42:1339. [PubMed: 2793587] (e) Shibata T, Kurihara S, Yoda K, Haruyama H. Tetrahedron. 1995; 51:11999.(f) Sekiyama Y, Palaniappan N, Reynolds KA, Osada H. Tetrahedron. 2003; 59:7465.(g) Choudhuri SD, Ayers S, Soine WH, Reynolds KA. J. Antibiot. 2005; 58:573. [PubMed: 16323318] (h) Mizuhara N, Usuki Y, Ogita M, Fujita K, Kuroda M, Doe M, Lio H, Tanaka T. J. Antibiot. 2007; 60:762. [PubMed: 18277002]

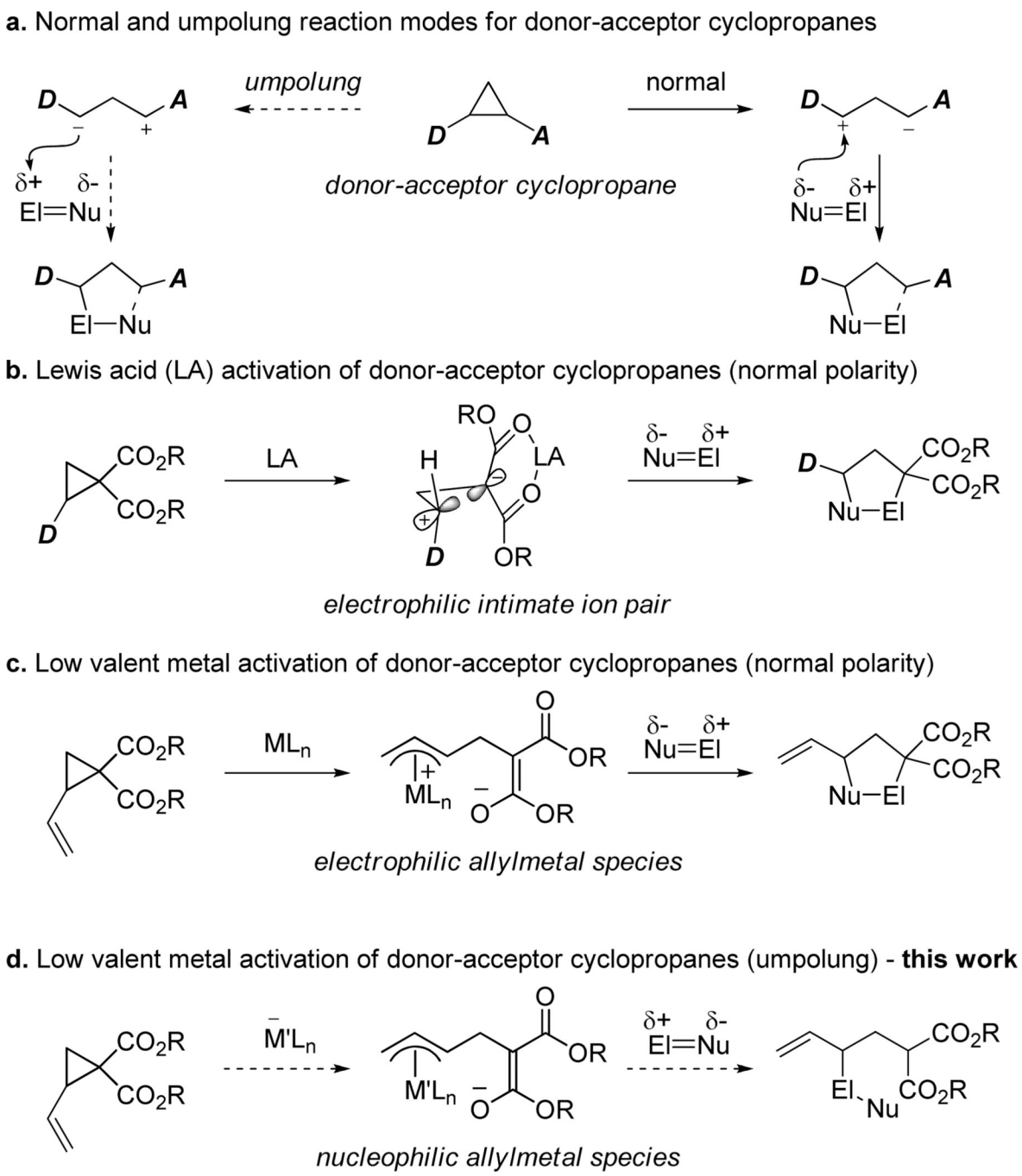
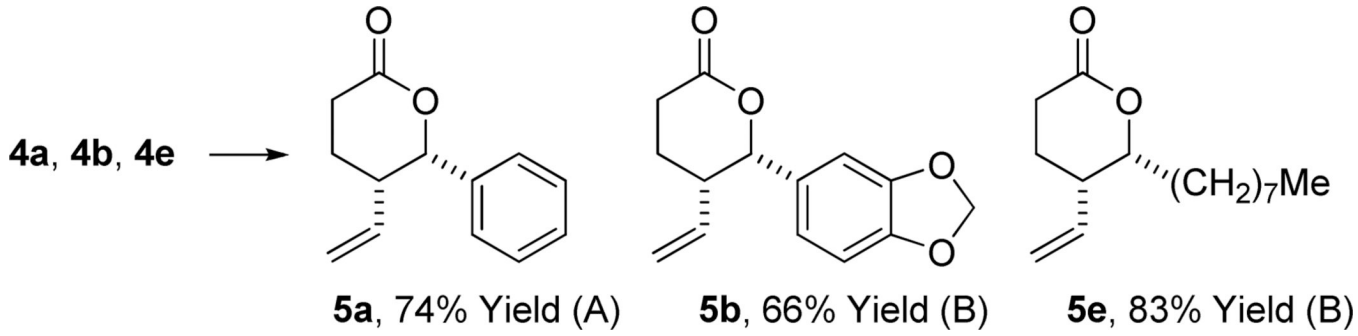


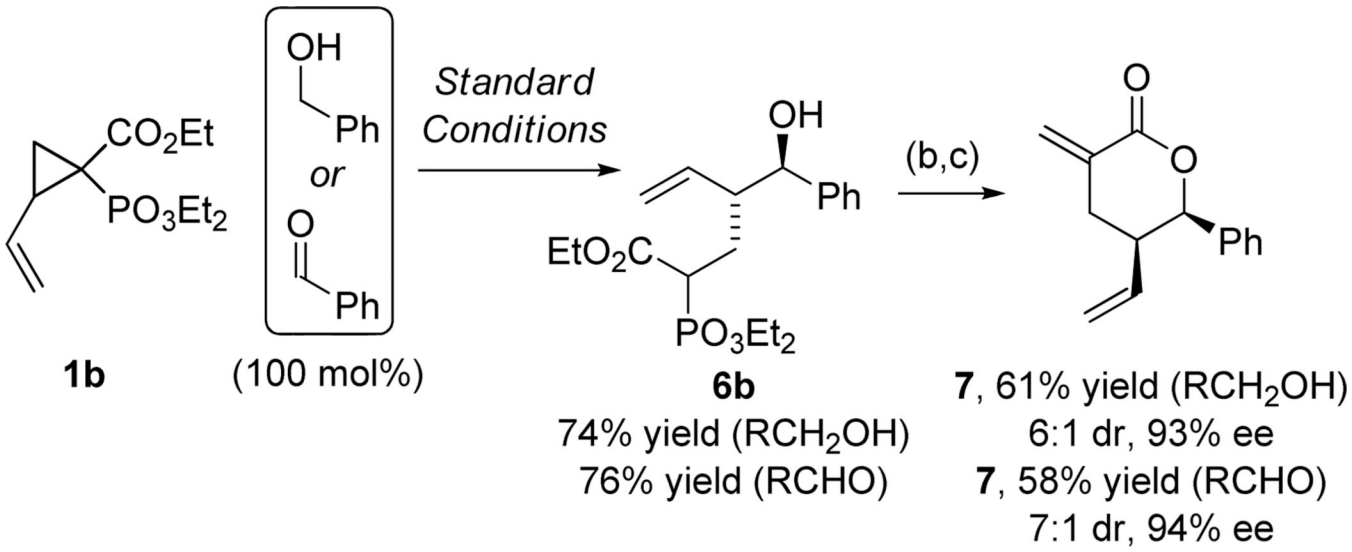
Figure 1.
Lewis acid and transition metal activation D-A cyclopropane methods of activation.



Scheme 1.

Formation of *cis*-4,5-disubstituted δ-lactones **5a, 5b** and **5e** *via* Krapcho decarboxylation.a

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



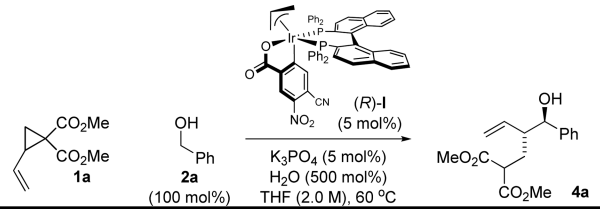
Scheme 2.

Reactions of D-A cyclopropanes **1b** which incorporates a phosphonoacetate.a

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

Table 1

Optimization of donor-acceptor cyclopropane-mediated carbonyl allylation of benzyl alcohol **2a**.[a]

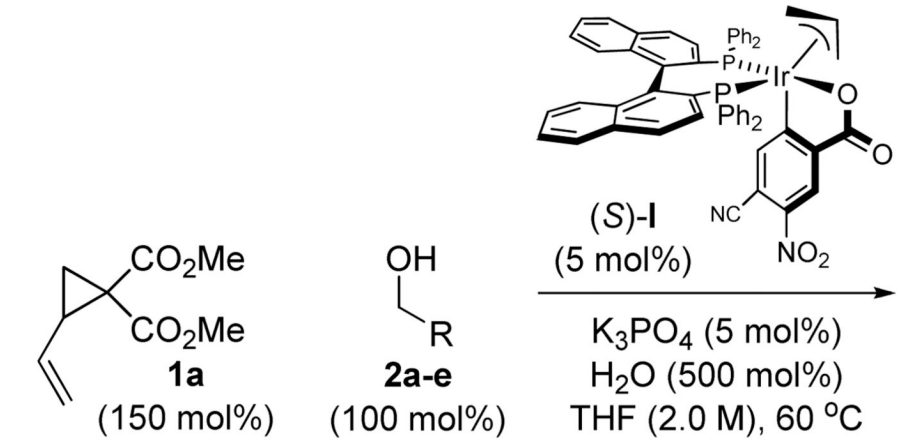


Entry	K_3PO_4 mol%	H_2O mol%	Temp. °C	1a mol%	Yield%	ee% (dr)
1	50	500	50	200	37	99 (>20:1)
2	0	500	50	200	0	N/A
3	5	500	50	200	81	98 (8:1)
4	5	0	50	200	0	N/A
5	5	500	60	200	84	98 (7:1)
6	5	500	60	150	84	98 (6:1)

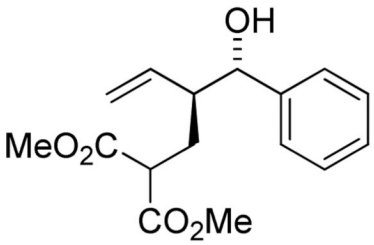
[a] Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details.

Table 2

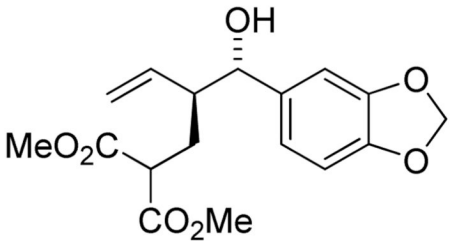
Donor-acceptor cyclopropane-mediated carbonyl allylation from the alcohol oxidation level.[a]



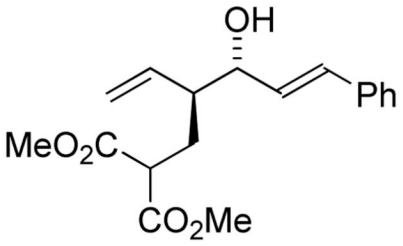
2a, R = Ph; **2b**, R = piperonyl; **2c**, R = (*E*)-CH=CH$_2$Ph; **2d**, R = geranyl; **2e**, R = *n*-octyl



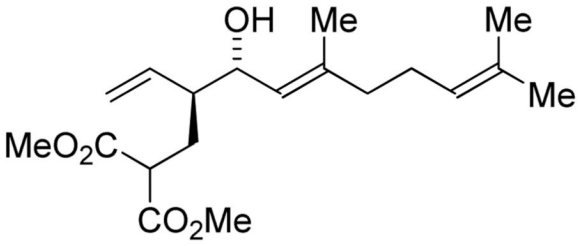
4a, 84% yield
6:1 dr, 98% ee



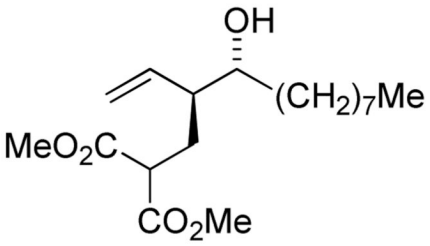
4b, 85% yield
7:1 dr, 96% ee



4c, 79% yield
6:1 dr, 93% ee



4d, 77% yield
9:1 dr, 91% ee

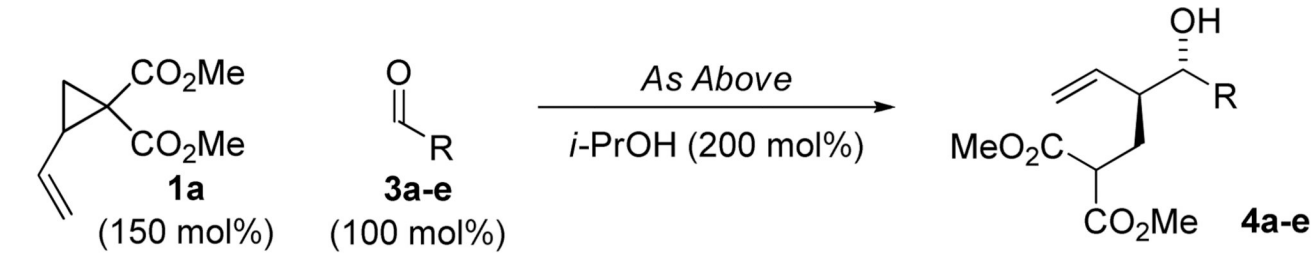


4e, 68% yield
6:1 dr, 98% ee

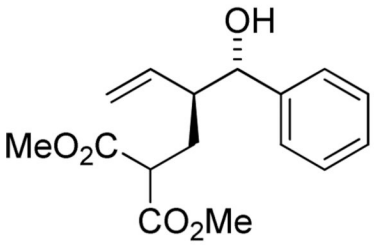
[a] As described for Table 1.

Table 3

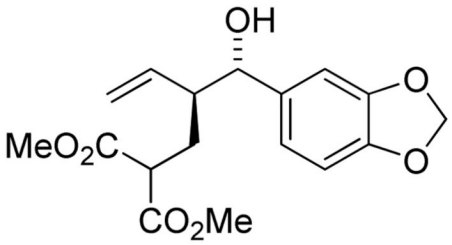
Donor-acceptor cyclopropane-mediated carbonyl allylation from the aldehyde oxidation level.[a]



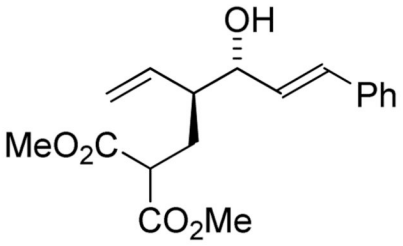
3a, R = Ph; **3b**, R = piperonyl; **3c**, R = (*E*)-CH=CH_2Ph; **3d**, R = geranyl; **3e**, R = *n*-octyl



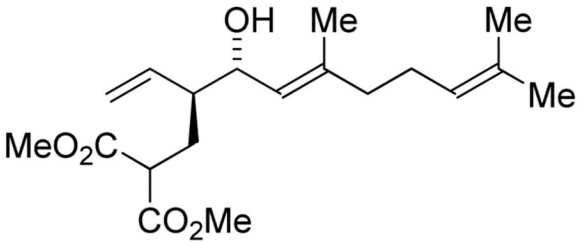
4a, 69% yield
>20:1 dr, 97% ee



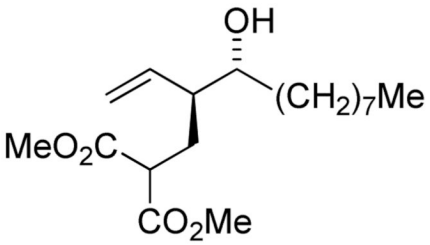
4b, 88% yield
18:1 dr, 97% ee



4c, 89% yield
17:1 dr, 97% ee



4d, 64% yield
>20:1 dr, 92% ee



4e, 63% yield
>20:1 dr, 97% ee

[a] As described for Table 1.