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Enantioselective Intermolecular Pd-Catalyzed Hydroalkylation of Acyclic 1,3-Dienes with Activated Pronucleophiles

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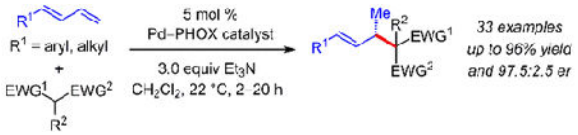
Abstract

We report a highly enantioselective Pd−PHOX-catalyzed intermolecular hydroalkylation of acyclic 1,3-dienes. Meldrum's acid derivatives and other activated C-pronucleophiles, such as β-diketones and malononitriles, react with a variety of aryl- and alkyl-substituted dienes in ≤20 h at room temperature. The coupled products, obtained in up to 96% yield and 97.5:2.5 er, are easily transformed into useful chemical building blocks for downstream synthesis.

Graphical abstract



The discovery of new methods for the enantioselective construction of C−C bonds is a critical objective in chemical synthesis, especially if novel transformations additionally offer access to new or expanded chemical space. Catalytic protocols are particularly desirable. A steadfast approach in C−C bond formation involves the enantioselective addition of polarized electrophiles to preformed enolates or their analogs. Alternatively, the direct addition of enolate precursors (pronucleophiles) to polarized reaction partners have also been developed. Aldol and Mannich reactions,[1] conjugate additions,[1a,b,e,2] allylic substitutions,[3] and alkylation with alkyl halides[4] comprise several examples.

Far less common are catalytic enantioselective additions of enols/enolates to simple unsaturated hydrocarbons. The Trost[5] and Luo[6] laboratories have reported Pd-catalyzed transformations involving terminal allenes. The Breit group has illustrated Rh-catalyzed reactions with 1,1-disubstituted allenes[7,8] and Dong and co-workers have described Rh-catalyzed reactions of methyl-substituted alkynes (Scheme 1).[9,10] These transformations

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ASSOCIATED CONTENT
Supporting Information
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Experimental procedures and analytical data for new compounds (PDF)
NMR spectra (PDF)

The authors declare no competing financial interest.

involve the intermediacy of a terminal metal−π-allyl complex. The resulting products contain a terminal olefin with an allylic stereogenic center or internal olefins with a homoallylic stereogenic center. Additionally, the Hartwig group has demonstrated Pd-catalyzed additions of two β-diketones to cyclohexadiene and 2,3-dimethylbutadiene.[11–14]

Our lab has recently disclosed highly enantioselective and efficient intermolecular additions of aliphatic amines to 1,3- dienes.[15] The reactions, promoted by an electron deficient Pd −PHOX catalyst, proceed via a 1,3-disubstituted Pd−π-allyl intermediate to generate myriad allylic amines. Herein, we demonstrate that Pd−PHOX catalysts permit the addition of a variety of activated C-pronucleophiles to several aryl- or alkyl-substituted acyclic dienes (Scheme 1). Reactions take place within 20 h at room temperature to generate products bearing internal olefins with allylic stereogenic centers by the formal addition of an enol across the diene's terminal olefin. Several transformations of the carbonyls and/or the olefins within the coupled products highlight the synthetic utility of the process.

We began by examining the coupling of Meldrum's acid **1a** and phenylbutadiene **2a** under previously established conditions for hydroamination (Table 1); however, none of the desired addition product **3a** was observed with **Pd-1** (entry 1). Reasoning that an ammonium salt might be needed as the acid source for Pd−H formation within the catalytic cycle, we explored the addition of amine base additives, which upon deprotonating **1a** would generate the corresponding ammonium enolate. Pleasingly, with Et_3N (2.0 equiv), **3a** is formed as the sole site isomer in 72% yield and 96.5:3.5 er (entry 2). Hünig's base (entry 3) offers identical enantioselectivity but higher yield of **3a** than Et_3N. DABCO also shows improved product yield and similar selectivity (entry 4). However, both bases consistently lead to lower product yields with other nucleophile classes.[16] DBU is ineffective (entry 5). We therefore chose to pursue Et_3N as the base of choice due to its generality. As little as 5 mol % Et_3N generates **3a**, but increasing the quantity of the base raises the reaction yield and enantioselectivity (entries 6−8). By introducing 1.5 equiv **1a** with 3.0 equiv Et_3N and increasing the reaction time to 15 h, **3a** was isolated in 81% yield and 97.5:2.5 er (entry 9). Neither lower temperature nor electronically modified phosphines (**Pd-2–3**) were able to improve upon this result (entries 10–13).[17]

With conditions determined for enantioselective hydroalkylation of **2a**, we next sought to discover the range of pronucleophiles that were amenable to the coupling (Table 2). Cyclic β-diketones[5b] efficiently undergo addition to phenylbutadiene to afford adducts **3b–d** in up to 95% yield and 96.5:3.5 er. Acyclic diketones[5b,7] also participate, delivering diones **3e–h** in 66–96% yield and 90.5:9.5 to 92:8 er and illustrating that both alkyl and aryl ketones are competent partners. Bis(sulfones) (**3i**), malononitrile (**3j**), and α-nitroesters (**3k**) all take part in diene hydroalkylation reactions. Dimethylmalonate (pK_a in DMSO = 15.9),[18a] however, fails to add to phenylbutadiene with the present catalytic system, suggesting an upper limit in pronucleophile acidity to between 14.2 (benzoylacetone **2h**)[18b] and 15.9. It should also be noted that products **3h** and **3k**, formed by the addition of prochiral nucleophiles to **2a**, are generated as a 1:1 mixture of diastereomers at the nucleophilic carbon; however, both stereoisomers are obtained with identical enantioselectivity in each case. In all cases, addition occurs across the diene's terminal olefin to form the illustrated product exclusively; the site selectivity is likely at least somewhat attributable to the PHOX ligand.[12b]

Substituted Meldrum's acid derivatives[5a,b] and malononitriles also participate in coupling with phenylbutadiene to deliver products that contain quaternary centers adjacent to the allylic stereogenic center (Table 3). The former's products **3l–o** are generated with modest efficiency but good enantioselectivity. These sterically congested pronucleophiles afford ca. 5% 1,4-addition product[16] with C–C bond formation occurring at the terminus of the diene. The enantioselectivity dependence on Et_3N equivalents is magnified in several cases with the Meldrum's acids **1l–o** compared to unsubstituted **1a:** with fewer equivalents of Et_3N, lower enantioselectivity is obtained, becoming even lower with longer reaction times.[16] In contrast, enantioselectivity is largely constant over the course of the reaction with 3.0 equiv Et_3N, suggesting less reaction reversibility under the optimized conditions.

Conversely, the less hindered substituted malononitriles couple with **2a** to deliver products **3p–s** in 77 to >98% yield within 2 h. In general, enantioselectivity is enhanced and the reactions show perfect site selectivity. Notably, unlike with Pd–bis(phosphine) catalysts, deallylation of malononitrile **1s**, which ultimately yields a statistical distribution of allylation products, does not occur with **Pd-1**. Prochiral pronucleophiles, such as *tert*-butyl cyanopropionate **1t**, also effectively add to diene **1a** but with little stereocontrol at the nucleophile's carbon (1.5:1 dr in forming **3t**); enantioselectivity of each diastereomer is substantial but unequal. Approximately 10% 1,4-addition accompanies the major product.

Several dienes have been examined for additions of Meldrum's acid (Table 4). Aryl-substituted dienes lead to styrenyl products **4a–d** in good yields (66–78%) within 15 h with **Pd-1** (96:4–97:3 er); however, an *o*-methyl group significantly slows the reaction (28% yield of **4e**; 97:3 er).[19] A furyl-substituted diene affords **4f** in 54% yield and 93:7 er. Just as in Pd–PHOX-catalyzed hydroaminations of these dienes,[15] the reaction is fastest with electron rich substrates, but unlike in amine–diene couplings, electron deficient or sterically hindered aromatic rings do not lead to 1,4-addition.

Alkyl-substituted dienes react sluggishly with Meldrum's acid when **Pd-1** is employed (ca. 50% yield in 15 h). Contrastingly, with the sterically less hindered **Pd-2**, reactions are complete within 6 h, affording unsaturated Meldrum's acids **4g–m** in 68–89% yield (Table 4). Unlike in reactions of aryl-substituted dienes, **Pd-2** is equally as enantioselective as **Pd-1** (93:7 to 95:5 er). Several functional groups are tolerated, including ethers (**4i**), imides (**4k**), and even free alcohols (**4j,l**).

The Meldrum's acid addition products provide a useful platform for accessing a number of β-methyl-γ,δ-unsaturated carbonyls. Ethanol addition to **3a**, prepared on 4.0 mmol scale, generates carboxylic ester **5a** in 96% yield (Scheme 2A).[20] Similarly, *N*-hydroxyphthalimide ester[21] **5b** (91% yield), carboxylic acid **5c** (79% yield), and Weinreb amide **5d** (74% yield) may be obtained. Products resulting from the addition of the unsubstituted malononitrile (e.g., **3j**, Scheme 2B) may undergo oxidation with MMPP and conversion to the methyl ester to furnish 6 in 63% yield,[22] which now bears a stereogenic center at the carbonyl's α-position. The transformation takes place with minimal erosion of enantiopurity. Additionally, the β-diketone scaffold may be utilized to generate heterocycles with α-stereogenic centers.[7,10c] For example, hydroxylamine condensation with diketone **3h** affords isoxazole **7** in 84% yield (Scheme 2C). The transformation significantly favors initial amine

attack upon the alkyl ketone (13:1 regioselectivity)[16] and ameliorates the lack of stereochemical control at the carbonyl's α-position in the hydroalkylation reaction by erasing the stereochemistry at the offending center.

The presence of both carbonyl and olefin functionality within the products may be leveraged to build molecular complexity quickly. The allylic hydroxyl group of **4l** may be selectively acylated and subjected to Pd-catalyzed allylic substitution in the presence of ethanol,[23] yielding γ-lactone **8** in 66% yield as a 7:1:1 mixture of diastereomers with the major isomer shown (Scheme 3A).[16] Additionally, Sharpless dihydroxylation of unsaturated ester **5a** with AD-mix β leads to spontaneous lactonization to afford γ-lactone **9** as the sole product of the reaction (70% yield, 19:1 dr, Scheme 3B).[16]

Highly efficient and enantioselective intermolecular addition of activated C-pronucleophiles to acyclic dienes is enabled by Pd catalysts bearing electron deficient phosphines within a PHOX ligand scaffold. A range of aryl- and alkyl-substituted dienes may be coupled with a number of β-dicarbonyl-like nucleophiles to generate allylic stereogenic centers at the carbonyl's β-position. The olefin and carbonyl functional groups provide handles for subsequent complexity-building product elaboration and access to useful synthetic motifs. Application of Pd–PHOX catalysts to other enantioselective hydrofunctionalizations is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. For details, see the Supporting Information.
17. Dienes with other substitution patterns, such as isoprene and 2,3-dimethylbutadiene, fail to undergo reaction with Meldrum's acid.
18. (a) Arnett EM, Maroldo SG, Schilling SL, Harrelson JA. J. Am. Chem. Soc. 1984; 106:6759.(b) Bordwell FG, Harrelson JA Jr. Can. J. Chem. 1990; 68:1714.
19. Product **4e** is generated in 82% yield and 82.5:17.5 er with **Pd-2**.
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22. Adapted from: Förster S, Tverskoy O, Helmchen G. Synlett. 2008:2803.
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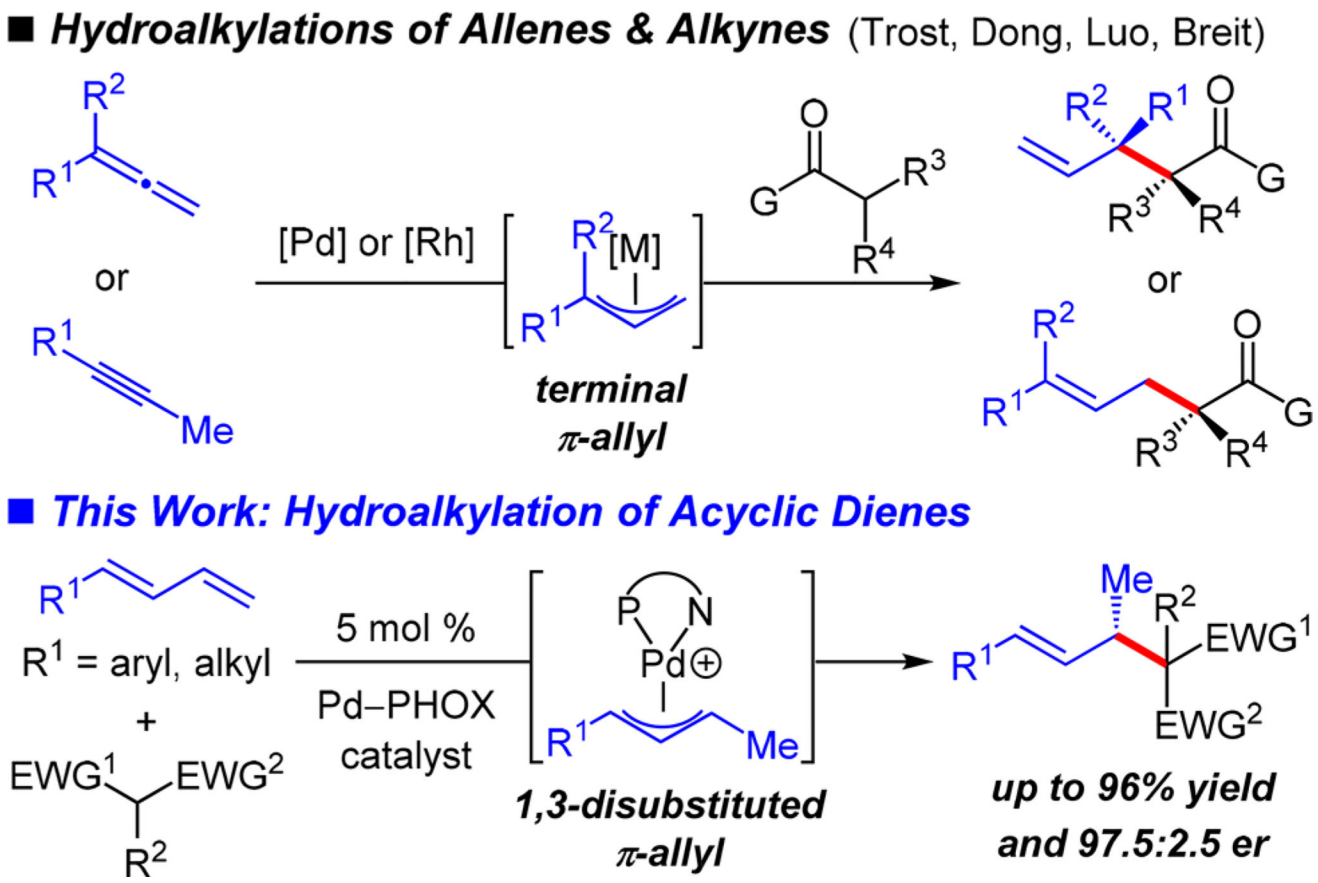
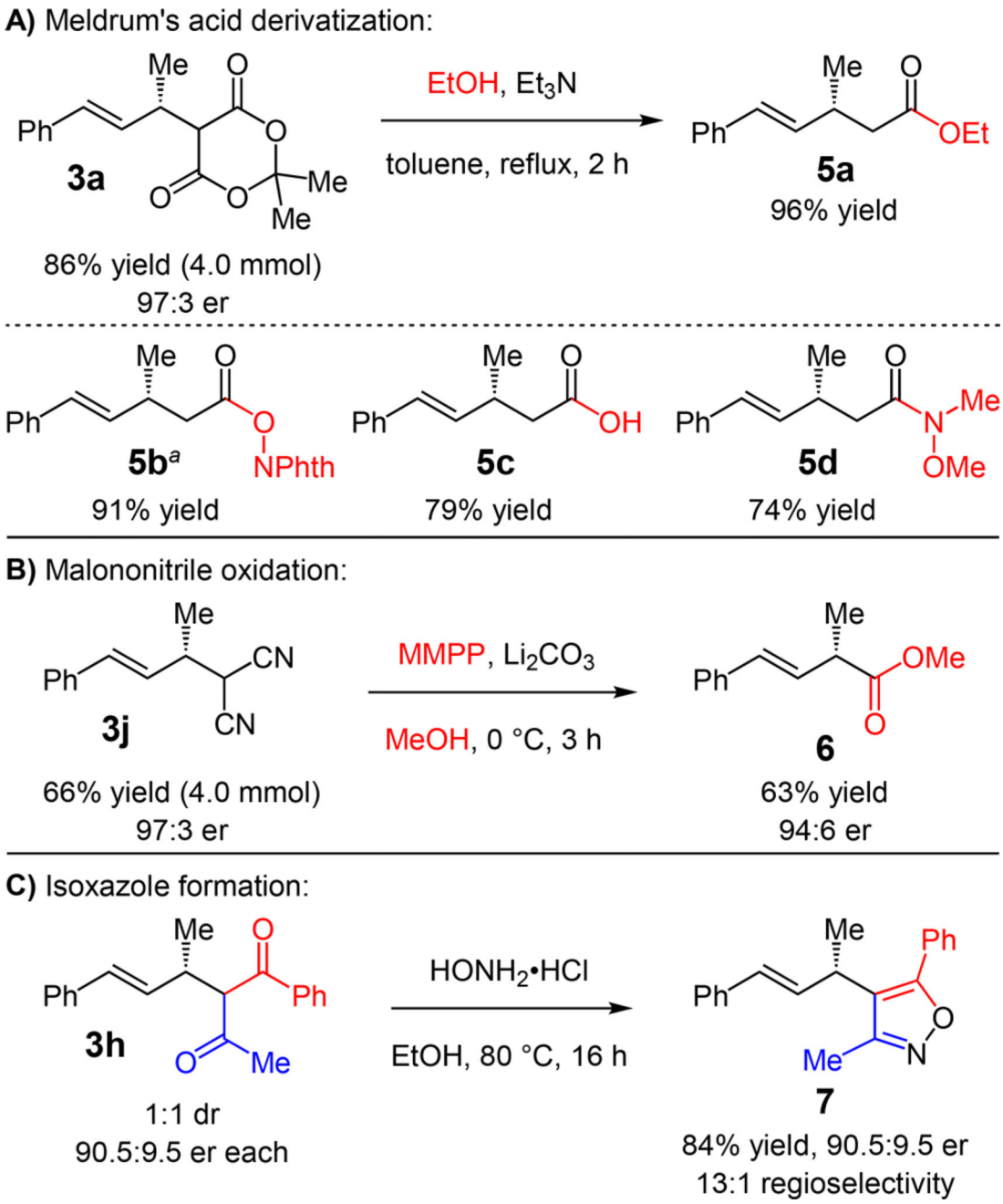


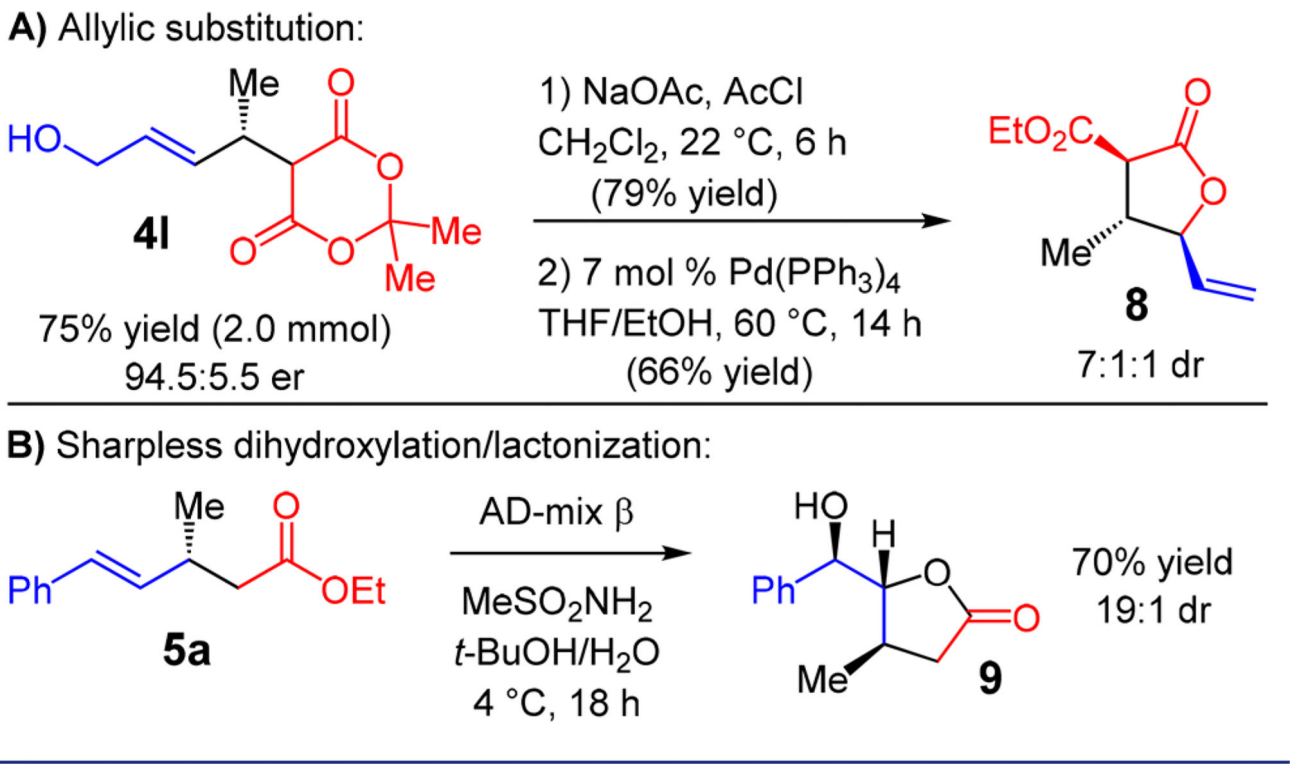
Scheme 1.
Previous and Present Work in Intermolecular Enantioselective Hydroalkylation



Scheme 2.

Carbonyl Functionalization within Coupled Products

[a]Reaction at 80 °C.



Scheme 3.
Simultaneous Carbonyl and Olefin Derivatization within Hydroalkylation Products

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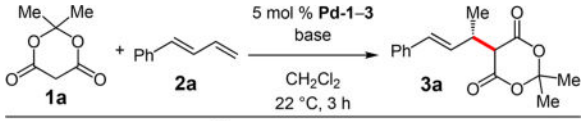
Table 1

Reaction Optimization for Meldrum's Acid Addition to Phenylbutadiene[a]



Pd-1 Ar = 3,5-$(CF_3)_2C_6H_3$

Pd-2 Ar = 4-$CF_3C_6H_4$

Pd-3 Ar = Ph

entry	catalyst	1a (equiv)	base (equiv)	yield (%)[b]	er[c]
1	**Pd-1**	1.1	none	<2	–
2	**Pd-1**	1.1	Et_3N (2.0)	72	96.5:3.5
3	**Pd-1**	1.1	*i*-Pr_2NEt (2.0)	82	96.5:3.5
4	**Pd-1**	1.1	DABCO (2.0)	88	95:5
5	**Pd-1**	1.1	DBU (2.0)	<2	–
6	**Pd-1**	1.1	Et_3N (0.05)	46	94:6
7	**Pd-1**	1.1	Et_3N (0.50)	51	95:5
8	**Pd-1**	1.1	Et_3N (3.0)	72	98:2
9[d]	**Pd-1**	1.5	Et_3N (3.0)	81	97.5:2.5
10[d,e]	**Pd-1**	1.5	Et_3N (3.0)	84	97.5:2.5
11	**Pd-2**	1.5	Et_3N (3.0)	95	93:7
12[e,f]	**Pd-2**	1.5	Et_3N (3.0)	89	96:4
13[d]	**Pd-3**	1.5	Et_3N (3.0)	80	94:6

[a] Reactions run with 0.2 mmol **2a** in 0.25 mL CH_2Cl_2.

[b] Isolated yield of **3a**.

[c] Enantiomeric ratio determined by HPLC analysis of purified products.

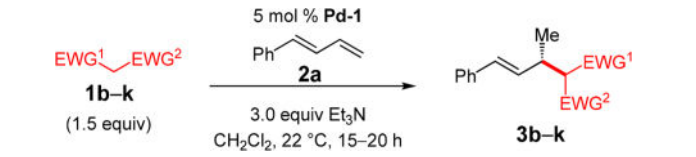
[d] 15 h reaction.

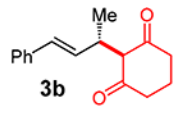
[e] 0 °C reaction.

[f] 16 h reaction.

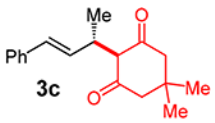
Table 2

Addition of Unsubstituted Pronucleophiles to Phenylbutadiene[a]

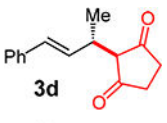




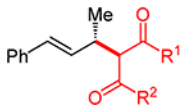
95% yield, 95.5:4.5 er



78% yield, 96.5:3.5 er



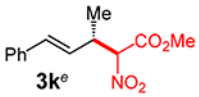
62% yield, 93:7 er



3e[d]	R^1, R^2 = Me:	90% yield, 92:8 er
3f	R^1, R^2 = Ph:	96% yield, 91.5:8.5 er
3g	R^1, R^2 = 4-$MeOC_6H_4$:	70% yield, 90.5:9.5 er
3h[e,f]	R^1 = Me, R^2 = Ph:	66% yield, 90.5:9.5 er

74% yield, 94:6 er

61% yield, 97.5:2.5 er



52% yield, 95:5 er

[a] See the Supporting Information for experimental details.

[b] Isolated yield of **3**.

[c] Enantiomeric ratio determined by HPLC analysis of purified products.

[d] BAr^F_4 counterion used in place of BF_4 for **Pd-1**.

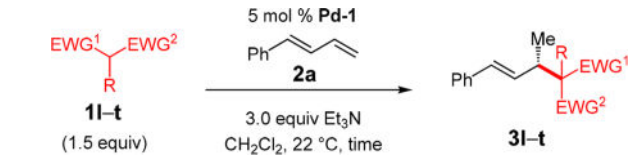
[e] 1:1 dr at carbonyls' α-position; both diastereomers have the same er.

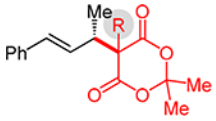
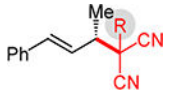
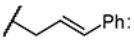
[f] 2.0 mmol scale reaction.

[g] 2 h reaction; ca. 20% double alkylation product.

Table 3

Quaternary Center Formation by Addition of Substituted Pronucleophiles to Phenylbutadiene[a–c]



	**3l**[d,e]	R = Me:	48% yield, 94:6 er
	3m[d,e]	R = Et:	37% yield, 91:9 er
	3n[d,e]	R = *n*-Bu:	33% yield, 91:9 er
	3o[d,e]	R = *i*-Pr:	29% yield, 88:12 er
	**3p**[f]	R= Me:	90% yield, 95:5 er
	3q[f]	R = *n*-Bu:	79% yield, 96:4 er
	3r[f]	R = Bn:	>98% yield, 94.5:5.5 er
	3s[f]	R =  Ph:	81% yield, 97.5:2.5 er
	**3t**[f]		80% yield, 1.5:1 dr, 10% 1,4-addition *major:* 94.5:5.5 er *minor:* 86:14 er

[a–c] See Table 2.

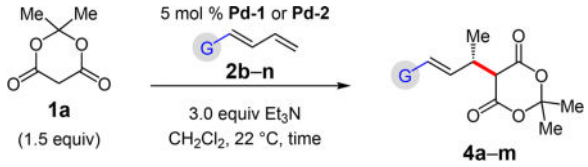
[d] Ca. 5% 1,4-addition observed.

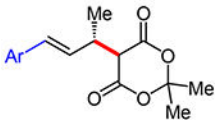
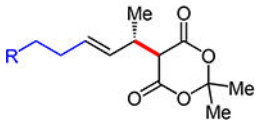
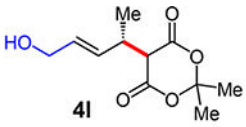
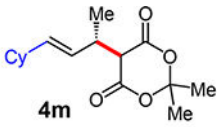
[e] 6 h reaction.

[f] 2 h reaction.

Table 4

Meldrum's Acid Addition to Various Aryl- and Alkyl-Substituted Dienes[a–c]



• *aryl-substituted dienes* with **Pd-1** (15 h) 	**4a**	Ar = 4-$MeOC_6H_4$	78% yield, 97:3 er
	4b	Ar = 4-ClC_6H_4	70% yield, 96.5:3.5 er
	4c	Ar = 4-$F_3CC_6H_4$:	66% yield, 96:4 er
	4d	Ar = 3-MeC_6H_4:	75% yield, 96.5:3.5 er
	4e	Ar = 2-MeC_6H_4	28% yield, 97:3 er
	4f	Ar = 2-furyl:	54% yield, 93:7 er
• *alkyl-substituted dienes* with **Pd-2** (6 h) 	**4g**	R = *n*-Bu:	68% yield, 95:5 er
	4h	R = Ph:	89% yield, 93.5:6.5 er
	4i	R = OTBS:	76% yield, 95:5 er
	4j	R = OH:	70% yield, 95.5:4.5 er
	4k[d]	R = NPhth:	85% yield, 95:5 er
 **4l** 77% yield, 94.5:5.5 er			
 **4m** 71% yield, 93:7 er			

[a–c] See Table 2.

[d] 1.0 equiv Meldrum's acid and 1.1 equiv diene **2l**.