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Enantioselective Construction of Quaternary Stereogenic Centers by the Addition of an Acyl Anion Equivalent to 1,3-Dienes

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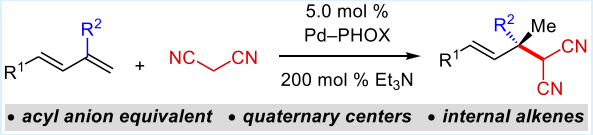
ABSTRACT: We report the enantioselective formation of quaternary stereogenic centers by the intermolecular addition of malononitrile, an acyl anion equivalent, and related pronucleophiles to several 1,3-disubstituted acyclic 1,3-dienes in the presence of a Pd–PHOX catalyst. Products are obtained in up to 88% yield and 99:1 er and in most cases are formed as a single regioisomer. The products' malononitrile unit undergoes oxidative functionalization to afford β,γ-unsaturated carbonyls bearing internal olefins and α-quaternary stereogenic centers.



The development of new catalysts and methods that enable the enantioselective formation of quaternary carbon stereogenic centers[1] is a critical endeavor in chemical synthesis as several natural products and other biologically active compounds contain such a motif.[2] Yet despite this need, the ability to prepare quaternary stereogenic centers enantioselectively within acyclic molecules is limited.[3] Particularly challenging in this regard is the synthesis of β,γ-unsaturated carbonyls, also called α-vinyl carbonyls; only a limited number of reports exist.[4]

One tactic in generating this functionality is allylic substitution.[4a,c] The Stoltz group has shown that a masked acyl cyanide (MAC) reagent, one type of acyl anion equivalent, combines with allylic carbonates in an enantioselective Ir–phosphoramidite-catalyzed process (Scheme 1A).[4c] Functionalization under acidic conditions gives rise to α-vinyl carboxylic acids and their derivatives.

An atom economic strategy for quaternary stereogenic center synthesis that has emerged recently is intermolecular hydrofunctionalization of unsaturated hydrocarbons by the addition of enol-type nucleophiles. This approach was first demonstrated by Trost and co-workers for cyclic quaternary stereogenic center formation in the Pd–bis(phosphine)-catalyzed addition of 3-aryl-2-oxindoles to alkoxyallenes (Scheme 1B).[5] In 2017, the Dong group developed a dual catalytic diastereodivergent method for coupling aldehydes to allylic electrophiles generated from alkynes, allowing for acyclic quaternary centers to be gained.[6−8] In both of these transformations, the quaternary centers formed are derived from the nucleophilic component.

In contrast, the laboratories of Breit[9] and Kang[10] independently accomplished the synthesis of quaternary stereogenic centers arising from the unsaturated hydrocarbon partner by the addition of enols/enolates to 1,1-disubstituted allenes (Scheme 1C). The authors showed four examples each. In these established hydrofunctionalizations, the use of enol-type nucleophiles leads to products that are composed of γ,δ-unsaturated carbonyls. Moreover, in each of these approaches, as in the allylic substitution illustrated in Scheme 1, the products bear only a terminal olefin adjacent to the quaternary center.[4d,e] Elaboration of this alkene to a more substituted analogue thus requires additional chemical steps,[11] and the most direct route—olefin cross-metathesis—would most likely be encumbered by the sterics of the quaternary center.[12]

We speculated that the regioselective hydroalkylation of 1,3-disubstituted acyclic dienes with malononitrile as an acyl anion equivalent[13] would enable the synthesis of α-vinyl carbonyl products bearing a quaternary stereogenic center *and internal alkenes* (Scheme 1D).[14] However, addition reactions involving dienes with this substitution pattern are uncommon,[15] and to the best of our knowledge, enantioselective nucleophilic additions are unknown.[16−18] Herein, we illustrate that malononitrile and similarly activated C-pronucleophiles couple regio- and enantioselectively with several dienes under the aegis of Pd–PHOX catalysis.[19]

We began by attempting the addition of malononitrile to diene (*E*)-**1a**, bearing a phenyl substituent at the 1,1-disubstituted olefin and a phenethyl group at the diene's terminus (Table 1). With PHOX-based catalyst **Pd-1**, 150 mol % of the diene, and 200 mol % Et_3N, the desired 4,3-addition product **2a** is obtained as the major isomer in 87% yield and 98.5:1.5 er (entry 1). Notably, the reaction affords a small quantity of product regioisomer **3a**.[20] In contrast to our previous findings in hydrofunctionalizations of terminal and 1,4-disubstituted dienes,[19,21] where the Pd–PHOX-catalyzed processes at times deliver product regioisomers arising from

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Scheme 1. Catalytic Enantioselective Synthesis of Quaternary Stereogenic Centers by Allylic Substitution with an Acyl Anion Equivalent and Hydroalkylation Processes

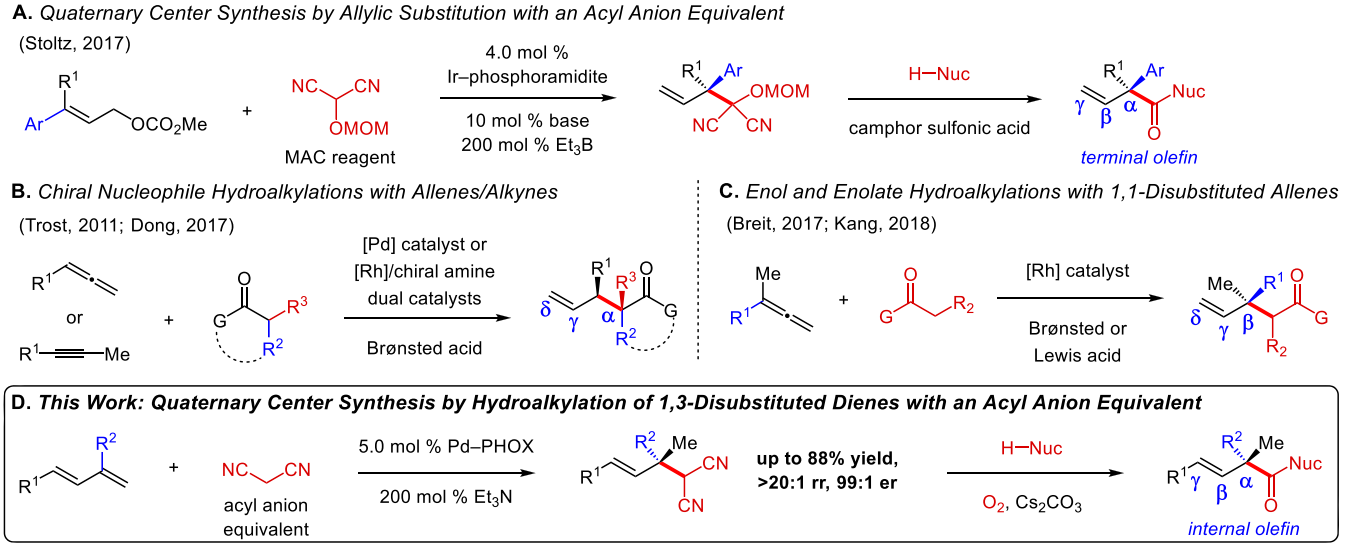
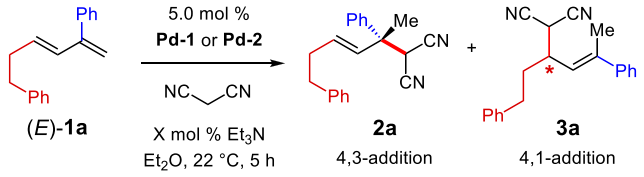
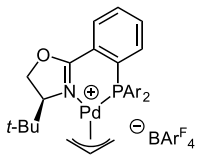


Table 1. Reaction Optimization for Malononitrile Additions to 1,3-Disubstituted Dienes[a]





Pd-1 Ar = 3,5-$(F_3C)_2(C_6H_3)$
Pd-2 Ar = 4-$F_3C(C_6H_4)$

entry	Pd	(*E*)-**1a** (mol %)	Et_3N (mol %)	**2a**:**3a**[b]	yield of **2a** (%)[c]	er of **2a**[d]
1	**Pd-1**	150	200	19:1	87	98.5:1.5
2	**Pd-2**	150	200	>20:1	80	98.5:1.5
3	**Pd-1**	150	100	18:1	84	98.5:1.5
4[e]	**Pd-1**	100	100	13:1	86	97.5:2.5
5	**Pd-1**	110	100	19:1	87	98.5:1.5

[a]Reactions run under N_2 with 0.2 mmol malononitrile (0.8 M). [b]Determined by 400 MHz ^1H NMR spectroscopy of the unpurified mixture. [c]Isolated yield of **2a** after purification. [d]Determined by HPLC analysis of purified **2a**. [e]150 mol % malononitrile (0.3 mmol).

hydrometalation of the two different olefins of the diene (4,3- and 1,4-addition products), the **2a**/**3a** mixture occurs only by reaction of the 1,1-disubstituted alkene of **1a**. Subsequent attack upon the two terminal carbons of the resulting unsymmetrical Pd–π-allyl intermediate generates the observed 4,3- and 4,1-addition products. The recovered diene **1a** is still >98% the *E*-isomer.

With **Pd-2** (entry 2), which differs from **Pd-1** by the aryl CF_3 group substitution pattern on the phosphine, **3a** cannot be detected; however, although enantioselectivity remains unchanged, the yield of **2a** is lower. This proved to be a general trend as yields from malononitrile additions to dienes **1** were lower in most cases by 5–10% with **Pd-2**. In some instances, enantioselectivities were also lower.[22]

Reducing the quantity of Et_3N had little effect on the malononitrile coupling to **1a** (entry 3). In contrast, employing the diene as the limiting reagent diminished both the regio- and enantioselectivity (entry 4). As shown in entry 5, having only a slight excess of the diene and 100 mol % Et_3N gave an identical result to the conditions in entry 1.

We next explored the scope of dienes amenable to malononitrile addition (Scheme 2). Although having no impact in the reaction of **1a**, adding only 110 mol % of diene and 100 mol % Et_3N in reactions of these other dienes diminishes the product yields.[22] Therefore, we employed the conditions in Table 1, entry 1, for expanding the substrate scope. While maintaining a phenyl substituent on the 1,1-disubstituted olefin, we examined various alkyl groups at R^1, with reactions leading to malononitriles **2b–g** in ≥98.5:1.5 er within 3 h. Linear, α-branched, and β-branched alkyl groups are well tolerated with malononitriles **2b–d** obtained in 70–88% yield. Under the mild reaction conditions, potentially labile groups such as a primary chloride (**2e**, 80% yield) and an allylic silyl ethers (**2f**, 81% yield) remain intact. A nitrogen heterocycle also does not interfere with the catalysis (**2g**, 88% yield). A pinacol boronic ester at R^1 in the diene allows for coupling to form alkenyl boron **2h** (44% yield and 99:1 er) with **Pd-2** as catalyst.[23]

Varying the aryl group identity while maintaining a phenethyl group at R^1 (dienes **1i–n**) results in a number of interesting findings related to arene electronics. With an electron-rich diene, such as anisole **1i**, only the desired regioisomer is formed (87% yield, 98.5:1.5 er after 3 h). A longer reaction time, however, results in markedly diminished enantioselectivity, suggesting reversibility of the product-forming step. Instead, transformations involving electron-poor dienes (e.g., **1j–k**) show a much slower erosion of er over time.[22] Simultaneously, regioselectivity is more modest with **1j–n** (4:1–16:1 **2**:**3**).[24] Yields and enantioselectivities remain excellent.

The positions of the aryl and alkyl groups within diene **1** may be switched to generate products comprised of alkyl-substituted quaternary centers. While still highly enantioselective at 4 °C (**2o–2q** formed in 93.5:6.5 to 94.5:5.5 er), the transformations are lower yielding than those with an aryl

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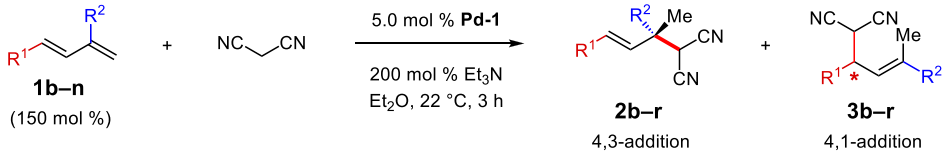
Scheme 2. Diene Scope for Malononitrile Addition Leading to the Formation of Quaternary Stereogenic Centers[a–d]



2b[e] R^1 = *n*-Pr: 78% yield, 99:1 er
2c[e] R^1 = *i*-Bu: 70% yield, 98.5:1.5 er
2d R^1 = Cy: 88% yield, 99:1 er

2e
80% yield, 98.5:1.5 er

2f
81% yield, 98.5:1.5 er

2g[e,f]
88% yield, 98.5:1.5 er

2h[g]
44% yield, 99:1 er

2i
87% yield, 98.5:1.5 er

2j
74% yield, 98:2 er
6:1 **2j**:**3j**

2k
78% yield, 98:2 er
5:1 **2k**:**3k**

2l
83% yield, 98:2 er
16:1 **2l**:**3l**

2m
72% yield, 98:2 er
4:1 **2m**:**3m**

2n[g]
69% yield, 96:4 er
10:1 **2n**:**3n**

2o[h]
40% yield, 93.5:6.5 er

2p[h]
37% yield, 94.5:5.5 er

2q[h]
43% yield, 94.5:5.5 er

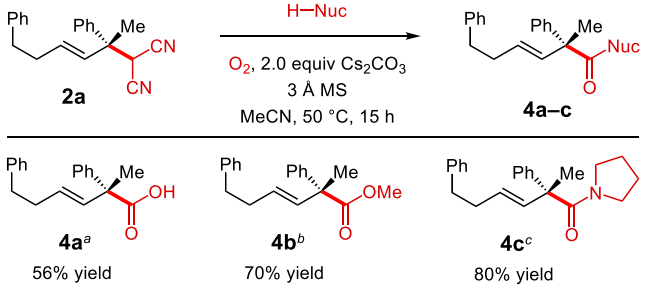
2r[h]
37% yield, 79.5:20.5 er

[a]Reactions under N_2 with 0.2 mmol of malononitrile (0.8 M). Dienes are 100% *E*-isomer unless otherwise noted; see the Supporting Information for details. [b]Ratio of **2**/**3** determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture and is >20:1 unless otherwise noted. [c]Isolated yield of **2** plus **3** after purification. [d]Er determined by HPLC analysis of purified **2** unless otherwise noted. [e]*E*/*Z* mixture of diene **1** was used. [f]Er determined after oxidative methanolysis of the malononitrile. [g]**Pd-2** used. [h]Reactions run in CH_2Cl_2 for 20 h at 4 °C.

group at the branched position. Although the yields can be slightly improved at room temperature with dienes **1o**–**1q**, the enantioselectivity suffers (e.g., **2o** is obtained in 53% yield and 92:8 er after 5 h at 22 °C). As product **2r** indicates (79.5:20.5 er), the R^2 alkyl group must be α-branched in order to attain high enantioselectivity.[25]

The capacity of the malononitrile group in the products (**2**) to undergo oxidative functionalization, thereby allowing its progenitor to function as an acyl anion equivalent, enables the synthesis of a variety of desirable carbonyl derivatives (Scheme 3).[13] With water, methanol, or pyrrolidine nucleophiles, carboxylic acid **4a**, ester **4b**, or amide **4c** are obtained in good yields under mild conditions. The resulting β,γ-unsaturated carbonyls, with their α-quaternary stereogenic centers, are thus easily furnished from 1,3-dienes by a two-step protocol.

Scheme 3. Oxidative Functionalization of Malononitrile-Containing Products



[a]With 10 equiv of H_2O and no molecular sieves. [b]With MeOH as the cosolvent. [c]With 2.0 equiv of pyrrolidine.

We additionally investigated the coupling of substituted malononitriles and other activated pronucleophiles to diene (*E*)-**1a** (Scheme 4). With sterically unhindered pronucleophiles, couplings are efficient: for example, 2-(methyl)- and 2-(cinnamyl)malononitrile lead to products **2s** and **2t**, containing vicinal quaternary centers,[26,27] in 78% and 64% yield, respectively. The MAC reagent[4c,28] delivers **2u** in 42% yield. An α-cyanoacetate nucleophile undergoes addition to (*E*)-**1a** to furnish **2v** in 82% yield (1:1 dr, 98.5:1.5 er), accompanied by a small quantity of regioisomer **3v**.

The initial stereochemical composition of diene **1a** has a large impact on reaction efficiency (eq 1). Compared to reaction of (*E*)-**1a** with malononitrile (Table 1, entry 1), the *Z*-isomer affords only 28% yield of **2a**. At the same time, a higher percentage of the product mixture is composed of the minor regioisomer (**3a**) when beginning with (*Z*)-**1a** (8:1 **2a**:**3a** versus 19:1 from (*E*)-**1a**), yet the identity of the major enantiomer of **2a** is the same in both cases. The recovered diene has not undergone any isomerization to the *E*-isomer. Collectively these data indicate that (1) diene hydrometalation with **Pd-1** is irreversible; (2) reactions of (*E*)- and (*Z*)-**1a** intersect the same Pd–π-allyl intermediate on the major

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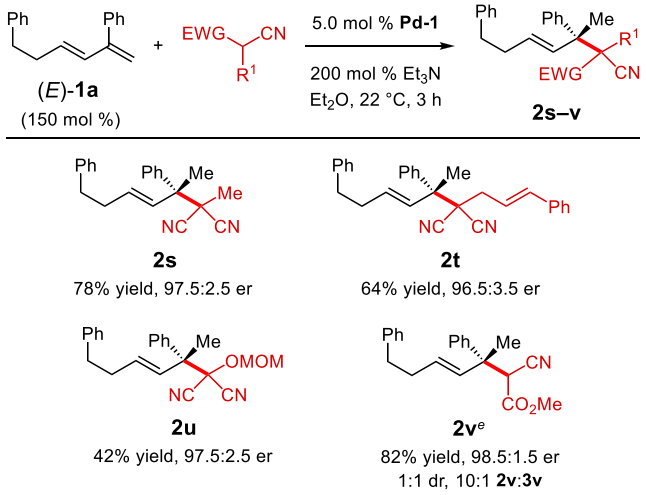
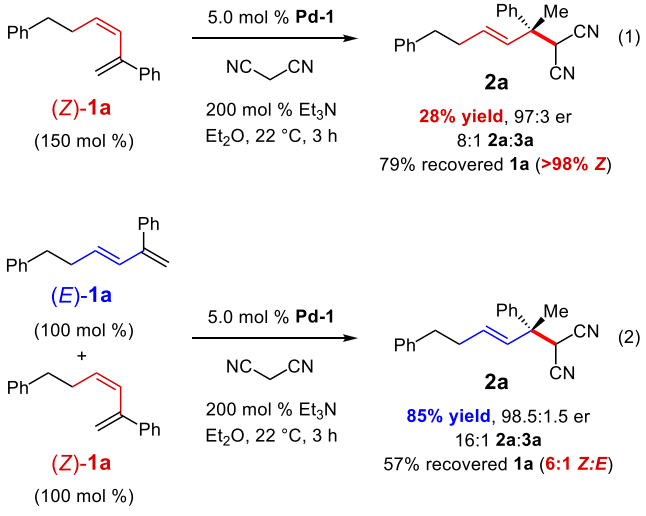
Scheme 4. Reactions of (*E*)-1a with Additional Pronucleophiles[a–d]



[a]Reactions under N_2 with 0.2 mmol of pronucleophile (0.8 M). [b]Regioselectivity determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture and is >20:1 **2**/**3** unless otherwise noted. [c]Isolated yield of **2** after purification. [d]Er determined by HPLC analysis of purified **2** except for **2v**, which was determined after hydrolytic decarboxylation of the methyl ester; see the Supporting Information. [e]Reaction in CH_2Cl_2; dr determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture.

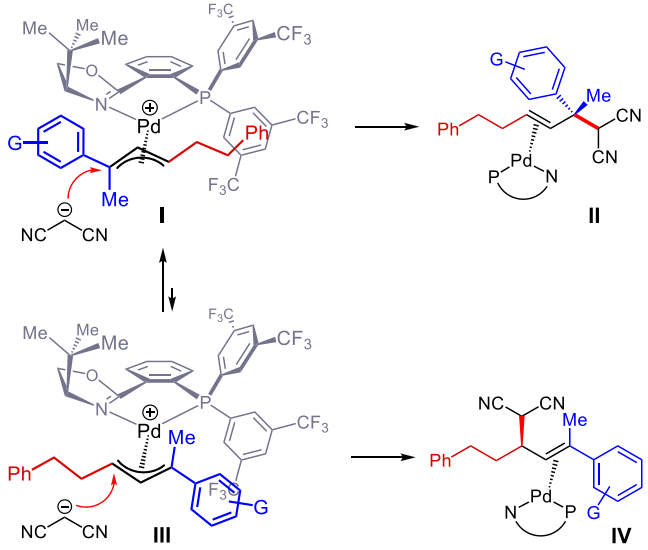


reaction pathway; and (3) the hydrometalation and/or isomerizations needed to convert (*Z*)-**1a** to this Pd–π-allyl are slower, resulting in lower yields and greater quantities of **3a** generated along the way.

Malononitrile addition to a 1:1 *E*/*Z* mixture of **1a** was also examined (eq 2) and demonstrates that the *Z*-diene does not impede the catalytic efficiency of **Pd-1** (cf. Table 1, entry 1). The recovered diene's 6:1 *Z*/*E* ratio (57% recovery) means that (*Z*)-**1a** essentially does not undergo reaction in this competition experiment. Therefore, either **Pd-1** must coordinate (*E*)-**1a** exclusively or (*E*)-**1a** must displace the *Z*-isomer from the metal prior to Pd–π-allyl formation.

The regio- and stereochemical course of the reactions could be rationalized as proceeding through Pd–π-allyl complex **I** (Scheme 5). Regardless of whether (*E*)- or (*Z*)-**1a** is employed, the same major enantiomer of the product is

Scheme 5. Proposed Regio- and Stereochemical Model for Malononitrile Additions



formed, thus illustrating that stereochemical equilibration of several allyl intermediates to **I**, wherein allylic strain is minimized, is faster than nucleophilic attack. This equilibration also explains the lower enantioselectivity observed in forming product **2r** bearing an isobutyl group, more similar in size to the π-allyl's geminal methyl substituent, compared to those compounds with α-branched alkyl groups (see Scheme 2, **2o**–**2q**). Pd(0) complex **II** with the metal coordinated to a disubstituted alkene—a likely driving force for the regioselectivity—is then formed en route to product **2**.

Complex **I** may equilibrate with π-allyl complex **III** via single bond rotation within an η^1-coordinated intermediate. Nucleophile attack upon **III** then affords Pd(0) species **IV**, having the metal coordinated to a more sterically hindered trisubstituted alkene, before forming product **3**.[20] As the diene's arene becomes more electron-poor, the transition state leading from **III** to **IV** may become more accessible due to increased olefin backbonding to Pd, overcoming the steric penalty (see Scheme 2). Finally, the identity of the catalyst, **Pd-1** or **Pd-2**, has little effect on product regioselectivity in most cases, regardless of electronics. However, regioselectivity is higher with **Pd-1** when the diene's aryl group is larger (e.g., **1l** or **1m**, Scheme 2), likely because of increased steric interactions within complex **III**.[22]

We have demonstrated for the first time that 1,3-disubstituted acyclic dienes may take part in highly efficient, enantio- and regioselective couplings with nucleophiles under mild conditions. Malononitrile, an acyl anion equivalent, and related pronucleophiles add regio- and enantioselectively across the 1,1-disubstituted olefin of 1,3-disubstituted dienes with a Pd–PHOX-based catalyst to deliver products bearing quaternary carbon stereogenic centers. These malononitrile adducts are easily converted to β,γ-unsaturated carbonyls comprised of α-stereogenic centers, thereby providing a modular two-step route to this challenging functionality.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00412.

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Experimental procedures, analytical data for new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(22) For additional details, see the Supporting Information.

(23) **Pd-1** leads to a lower yield in this instance.

(24) Although the yields provided are for the regiomeric mixture, in most cases, isomers **2** and **3** could be separated. The er for isomer **3** was equally high; see the Supporting Information.

(25) 1,3-Dialkyl-substituted 1,3-dienes are unreactive, and 1,3-diaryl dienes proved too unstable for study.

(26) For related examples in allylic substitution, see: Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Enantioselective Synthesis of Vicinal All-Carbon Quaternary Centers via Iridium-Catalyzed Allylic Alkylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 8664−8667.

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