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Pd-Catalyzed Heck-Type Reactions of Allenes for Stereoselective Syntheses of Substituted 1,3-Dienes

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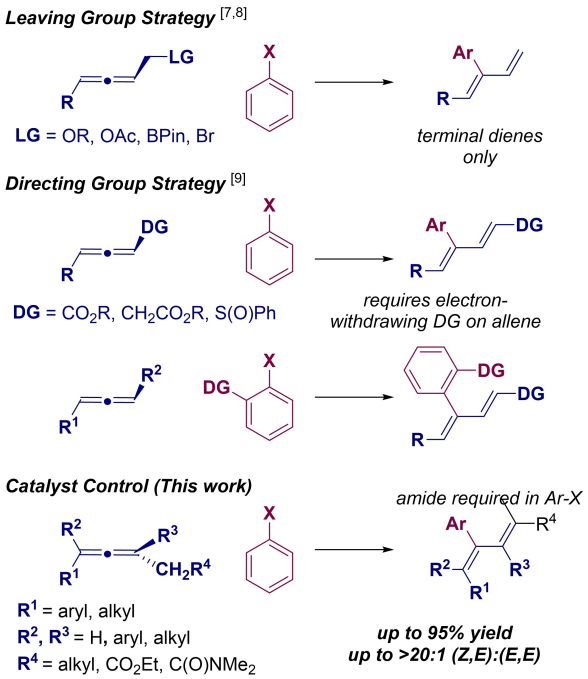
Abstract: A highly stereoselective Pd-catalyzed Heck-type reaction of allenes in which the stereochemistry of both olefins is set simultaneously was developed. The ligand CyJohnPhos was crucial to achieving stereoselectivity, while minimizing isomerization of the starting material through hydropalladation. The stereodetermining factors were proposed to be $A^{1,3}$ strain between the catalyst and allene substituent, which influences the σ-π-σ equilibrium of the coupled allene intermediate, as well as eclipsing interactions of R groups in the β-hydride elimination. Good functional group tolerance and stereoselectivities for formation of the *Z,E* isomer were demonstrated. The methodology was further expanded to include the regioselective formation of 2,4-dienoates and 2,4-dienamides with a variety of substitution patterns, albeit in reduced stereoselectivities favoring the *E,E* isomer. A plausible mechanism is proposed to account for the observed selectivities and substituent effects.

The 1,3-diene motif has been a key synthetic building block for over 100 years, arguably beginning in 1910 with Lebedev's preparation of the first butadiene-based polymer.[1] The report of the venerable Diels-Alder reaction further increased the significance of 1,3-dienes;[2] to this day, they enjoy wide application in pericyclic reactions and serve as precursors for transformations that include hydrofunctionalizations, aminohydroxylations, Morita-Baylis-Hillman, and Heck reactions.[3] The motif also occurs frequently in bioactive natural products and pharmaceuticals, including Vitamin A, abscisic acid, and (*S*)-methoprene. The broad utility of 1,3-dienes has inspired the development of diverse methods for their synthesis, including Wittig olefination and related reactions, enyne metathesis, Claisen rearrangements, alkyne isomerization and cross-coupling reactions.[4] However, these strategies are often more reliable for furnishing less-substituted dienes; attempts to extend these methods to the preparation of highly substituted 1,3-dienes often results in loss of stereo- and regiochemical control. Traditional transition metal-catalyzed cross-couplings focus on the formation of the central single bond of the 1,3-diene, but require stereodefined olefins functionalized with either an electrophilic or metal substituent. Metal-catalyzed ene-yne cross-coupling of alkenyl halides or conjugated alkenes with alkynes offer an alternative approach; however, many of these methods rely on symmetrical alkynes to avoid issues with regioselectivity.[5] In 2014, Zhao reported an excellent alkyne-alkenyl ester coupling to form 2,4-dienoates in a stereo- and regioselective manner; however, only a single substitution pattern could be accessed, as terminal alkynes gave low yields and no substitution on the alkenyl ester was demonstrated.[6]

There are scattered examples utilizing allenes as precursors for the stereoselective formation of 1,3-dienes (Scheme 1).[7] Simple allene isomerization is one option; however, it lacks the potential to build molecular complexity into the product. Other methods to synthesize 1,3-dienes from allenes use pre-installed leaving and directing groups to drive both reactivity and selectivity. For example, in 2010, Murakami reported Rh-catalyzed couplings of allenyl alcohols and boronic acids to prepare 1-aryl-1,3 dienes via a δ-oxygen elimination.[8] Various dehydrogenative couplings of allenes have also been reported using Rh and Ag cocatalysts and superstoichiometric transition



Scheme 1. Syntheses of 1,3-dienes from allenes.

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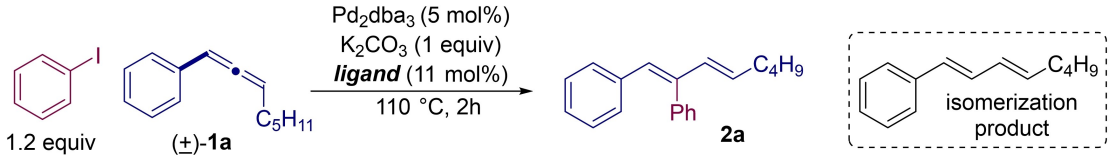
metal oxidants; these methods typically use a terminal allene and require a directing group on the coupling partner and/or substrate.[9] The vast majority of previously reported transformations also employ expensive rhodium catalysts. We envisaged a Heck-type coupling of highly substituted allenes would offer facile access to valuable 2-aryl-1,3-dienes from readily accessible precursors and catalysts. In addition, the ability to simultaneously set the stereochemistry of both olefins in the 1,3-diene without the need for a preinstalled functional handle would be a major advance. In this communication, we harness $A^{1,3}$ strain and eclipsing interactions in the key stereodetermining intermediate of a Pd-catalyzed Heck-type coupling of unadorned allenes to control the stereochemistry of each olefin in the 1,3-diene products. This stereoselective method was also expanded to include the regioselective syntheses of 2,4-dienoates and dienamides.

We began our investigations by targeting a stereoselective reaction of **1a**, where regioselectivity in the final β-hydride elimination is not an issue, as only one substituent bears a β-hydrogen group. $Pd(PPh_3)_4$ was employed as the initial catalyst using K_2CO_3 as a base and iodobenzene as the coupling partner. As Heck reactions often require elevated temperatures, the reaction was run in dimethylformamide (DMF) at 110 °C to afford **2a** in 76% yield (Table 1, entry 1), albeit in only a 4.3:1 (*Z,E*):(*E,E*) ratio. The Pd source was changed to Pd_2dba_3 (dba, dibenzyl-ideneacetone) to enable exploration of ligand effects. Unfortunately, triarylphosphines (Table 1, entries 2–4) gave reduced reactivity and little-to-no improvement in stereoselectivity. The use of bidentate phosphine ligands largely restored the reactivity, but the stereoselectivities (Table 1, entries 5–6) were still moderate. The bulk of the ligand was then systematically increased by replacing the aryl phosphine substituents with cyclohexyl groups. Ligands bearing mixed alkyl/aryl phosphines showed increased stereoselectivity to 6.6:1 (*Z,E*):(*E,E*) for PPh_2Cy (Cy, cyclohexyl) and 12.9:1 (*Z,E*):(*E,E*) for CyJohnPhos (Table 1, entries 7 and 9); in both cases, the use of excess ligand had little effect (Table 1, entries 8 and 10). PCy_3 as a ligand displayed excellent *(Z,E):(E,E)* stereoselectivity, but unproductive isomerization was the dominant reaction pathway (Table 1, entry 11). We were delighted to find that decreasing the temperature to 80 °C improved the yield to 82% and furnished >20:1 *(Z,E):(E,E)* selectivity (Table 1, entry 12). Further decrease in temperature had a negative impact on reactivity and selectivity (Table 1, entry 13).

With optimized conditions in hand, the scope of the reaction was explored, beginning with the aryl iodide coupling partner. Aryl iodides bearing electron-deficient groups *para* to the halogen, including esters, ketones, aldehydes, and trifluoromethyl groups (Table 2, entries **2b**–**2e**) were well-tolerated, delivering good yields and good-to-excellent *(Z,E):(E,E)* ratios. Electron-rich 2- and 4-iodoanisoles gave reduced yield and selectivity (Table 2, entries **2f**–**2g**) even at higher temperatures, while 3-iodoanisole gave good yield and selectivity (Table 2, entry **2g**). This negative impact likely arises from delocalization of the oxygen lone pair into the aryl ring, influencing proposed intermediates **7a**–**c** (Scheme 2, see

Table 1. Catalyst optimization studies.



entry	Ligand	yield (%)[b]	(*Z,E*):(*E,E*)	isom (%)	rsm (%)
1	$Pd(PPh_3)_4$[a]	76	4.3:1	4	--
2	**A**	62	5.0:1	*trace*	20
3	**B**	15	7.9:1	4	80
4	**C**	22	2.6:1	5	75
5	dppm	57	4.3:1	6	8
6	dppf	72	8.3:1	4	--
7	PPh_2Cy	75	6.6	11	--
8	PPh_2Cy[c]	74	6.1	9	--
9	CyJohnphos	68	12.9:1	14	--
10	CyJohnphos[c]	67	13.4:1	14	--
11	PCy_3	23	>20:1	66	--
12	**CyJohnphos**[d]	82	>20:1	10	--
13	CyJohnphos[e]	37	13.0:1	4	34

[a] no Pd_2dba_3 [b] ^{1}HNMR yield determined by $SiMe_3Ph$ standard
[c] 20 mol% ligand [d] run at 80 °C for 16 h [e] run at 65 °C for 16 h

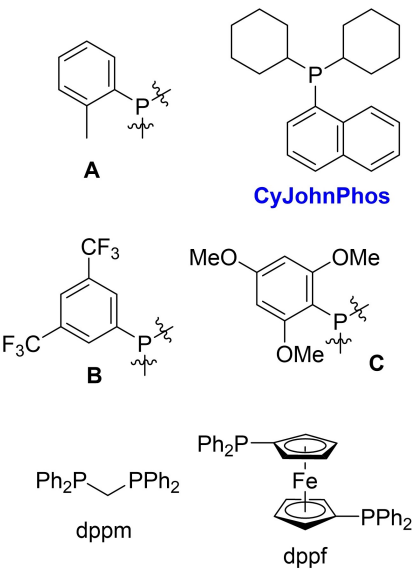
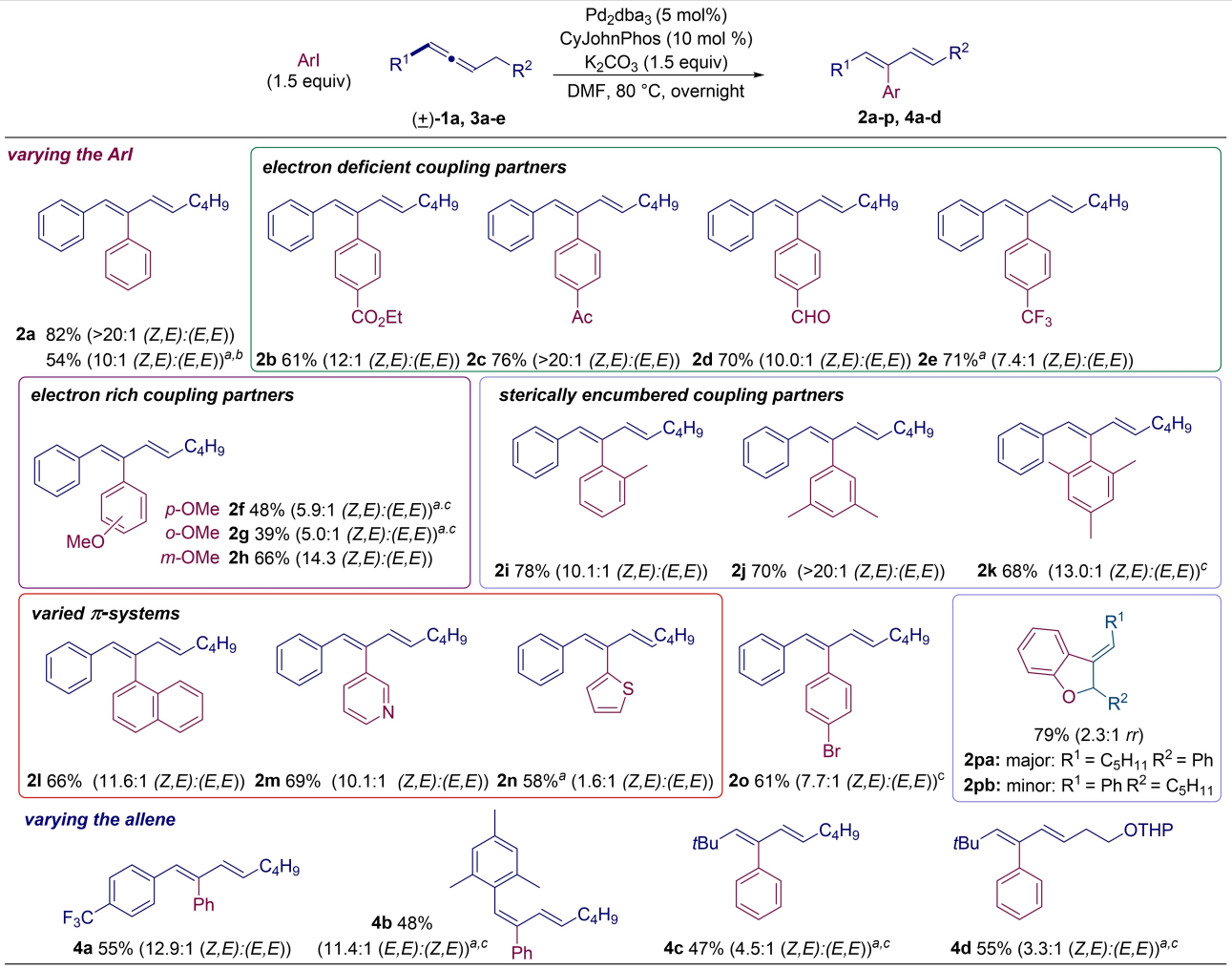


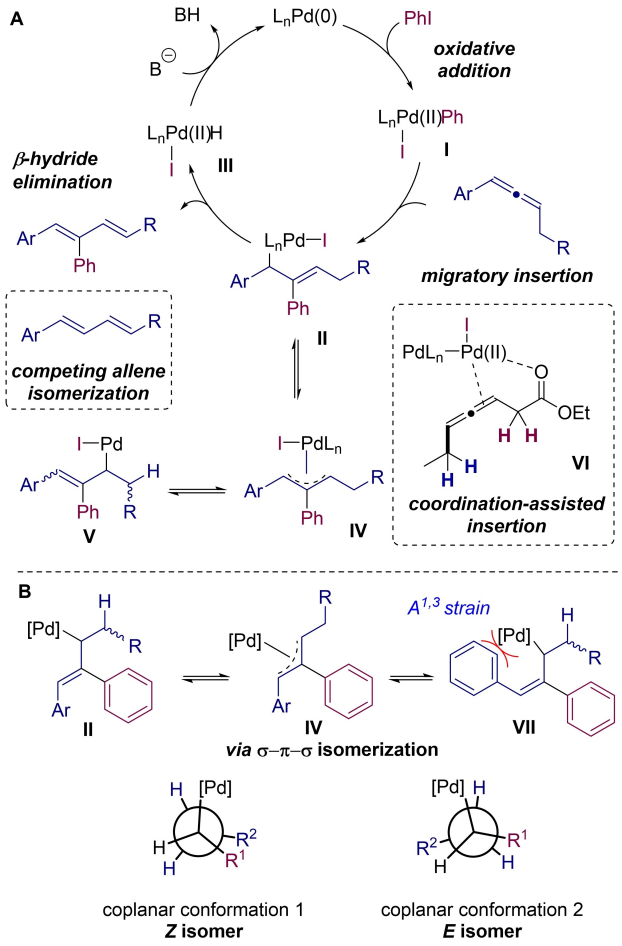
Table 2. Scope of Pd-catalyzed synthesis of (*Z,E*)-1,3-dienes.



[a] Yield determined by ^{1}HNMR with mesitylene internal standard. [b] Bromobenzene used as coupling partner. [c] Run at 110 °C.

below). Sterically encumbered aryl iodides (Table 2, entries **2i**–**2l**) gave good yields and excellent stereoselectivities, although some cases required elevated temperatures to push the reaction to completion. Extended π-systems and heterocycles, including 1-iodonaphthalene and 3-iodopyridine, were also tested and delivered good yields and *(Z,E):(E,E)* selectivities. However, 2-iodothiophene provided **2n** (Table 2) with a sharply reduced (*Z,E*):(*E,E*) ratio. Bromobenzene was tested to explore whether the method could be expanded to other aryl halides, however, lower yields and increased isomerization resulted (Table 2, entry **2a**′). However, when 1-bromo-4-iodobenzene was run at 110 °C, the diene **2o** (Table 2) was formed in good yield with moderate stereoselectivity, showing a tolerance for valuable halogen functional handles. Interestingly when 2-iodophenol was used as the substrate, benzofurans **2pa** and **2pb** (Table 2) were observed in 79% total yield (2.3:1 *rr*). This is likely the result of a nucleophilic cyclization of η^3-π-allyl intermediate **IV** (Scheme 2, see below) that directly reduces the Pd(II) intermediate back to Pd(0) to close the catalytic cycle. Finally, we explored different allenes to assess their impact on the reaction outcome. Electron-deficient diene **4a** (Table 2) was successfully formed in a 55% yield from a trifluoromethyl substituted diene in a very good 12.9:1 (*Z,E*):(*E,E*) ratio. Interestingly, sterically encumbered diene **4c** was formed in a 48% yield, but favored the (*E:E*) isomer. This is likely due to steric interactions that force the mesityl group out of conjugation, irrespective of the olefin stereochemistry. In this case, the mesityl is directed away from the Pd-catalyst in the *E* conformation, significantly reducing the $A^{1,3}$ strain and rendering the steric interactions between the olefin substituents the stereodetermining factor. Finally, *t*Bu bearing allenes were tested to give dienes **4d** and **4e** (Table 2) with moderate yields and stereoselectivities, **4e** also demonstrated a tolerance of THP-ethers.

Allene precursors in which both sides of the allene possess a hydrogen that may compete for β-hydride elimination represent more challenging substrates for our methodology. A variety of allenyl esters and amides with different substitution patterns were prepared and subjected to the optimized reaction conditions (Table 3). We were pleased to find that in all

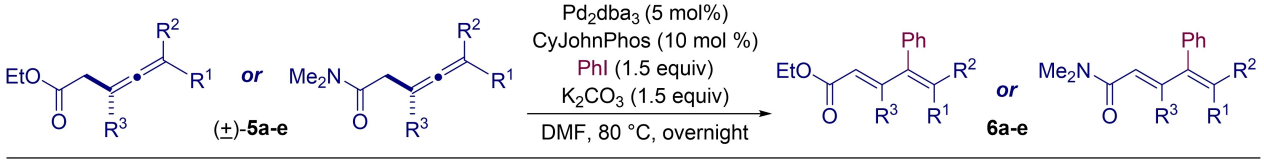


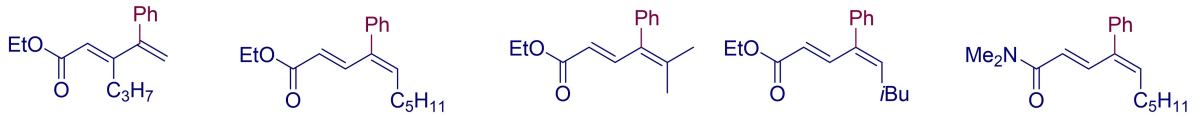
Scheme 2. Proposed mechanism and stereodetermining model.

cases, exclusive formation of the coupled 2,4-dienoate or dienamide was observed in good-to-excellent yields. Substitution was tolerated at both the proximal and distal allene carbons to the esters of **5a–b** to furnish **6a–b** (Table 3). Disubstitution and branching were also tolerated at the distal carbons in **5c–d** to give **6c–d** (Table 3), indicating that the reaction is not sensitive to the sterics of the allene and is capable of delivering valuable tetrasubstituted olefins. While dienoates with symmetric terminal olefins yielded a single stereoisomer, non-symmetric 2,4-dienoates showed poor stereoselectivity at the distal olefin, although the olefin formed via β-hydride elimination maintained exclusive *E* stereochemistry. Allenyl amide **5e** was also tested and shown to exclusively yield the 2,4-dienamide **6e** (Table 3). The utility of these products was shown with post-functionalization including Sharpless asymmetric dihydroxylation, Diels-Alder cycloaddition, and dibromination (Figure S1 in the Supporting Information).

A plausible mechanism is illustrated in Scheme 2A. The first step involves oxidative addition of Pd(0) into the aryl iodide to give **I**. After coordination to the allene, migratory insertion into one of the allene C–C π-bonds gives **II**, which is likely in equilibrium with **IV** and **V** via a σ-π-σ isomerization process (Scheme 2B). Steric and electronic factors compete to shift this equilibrium amongst **II**, **IV** and **VII** in the stereochemical-determining step. The dominant factor for formation of the *cis* relationship between the two aryl groups is likely minimization of $A^{1,3}$ strain between the aryl group on the allene precursor and the catalyst to favor **II** over **VII**. This effect is increased due to the energetic benefit of extended conjugation when remaining planar or near planar. Subsequent β-hydride elimination furnishes the *E* stereochemistry at the second alkene of the 1,3-diene product, in line with typical Heck couplings; final reductive elimination of **III** with base regenerates the active Pd(0) catalyst. The observation that strong electron-donating groups on the aryl iodide coupling partner (Table 2, **2f–g**) leads to poor yield and stereoselectivity is hypothesized to be due to inhibition of isomerization to **IV** by increasing conjugation in the stilbene moiety. In the case of benzofurans **2pa** and **2pb**, it is possible the phenol or phenoxide cyclizes onto the π-allyl intermediate **IV**, accounting for the disparity in reactivity compared to 2-iodoanisole. The selectivity observed for reactions of 2,4-dienoates and dienamides can be rationalized through coordination-assisted insertion of the Pd into the C=C bond (**VI**) to influence the regioselectivity of the migratory insertion and/or the σ-π-σ equilibrium.

Table 3. Scope of Pd-catalyzed synthesis of 2,4-dienoates and 2,4-dienamides.





6a 88% (>20:1 *E*:*Z*) | **6b** 82% [1.1:1 *(E,E):(Z,E)*] **6b** 88% [1.0:1 *(E,E):(Z,E)*][a] | **6c** 71% (>20:1 *E*:*Z*) | **6d** 95% [2.9:1 *(E,E):(Z,E)*] | **6e** 85% [1.3:1 *(E,E):(Z,E)*]

[a] Run on 0.5 g scale with 2.5% Pd_2dba_3 and 5.5% CyJohnPhos.

Formation of the competing allene isomerization product (Scheme 2A) arises from slow reductive elimination of hydrogen iodide from **III**. This leads to competing hydropalladation of the allene precursor by **III**, leading to isomerization with no desired coupling. This correlates with our observations that electron-rich phosphines (PCy_3, Table 1, entry 11), which favor $L_nPd(H)I$ over $L_nPd(0) + HI$, lead to significantly more isomerization, as compared to coupling.

In conclusion, we have developed a Pd-catalyzed Heck-type reaction of allenes that delivers highly substituted 1,3-dienes with good *(Z,E):(E,E)* stereoselectivities, as well as 2,4-dienoates and 2,4-dienamides with excellent regioselectivity. The methodology tolerates a wide variety of substitution patterns and coupling partners without the need for a pre-installed directing or leaving group. The stereoselectivity of the styrenyl moiety is achieved as a result of $A^{1,3}$ strain influencing the σ-π-σ equilibrium, however some coupling partners such as resonance donors inhibited this isomerization leading to low stereoselectivities. Eclipsing steric interactions reliably set the stereochemistry of the olefin formed by β-hydride elimination regardless of substrate and coupling partner.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: allene · 1,3-dienes · 2,4-dienamides · 2,4-dienoates · Heck coupling

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