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Sulfinate-Engaged Nucleophilic Addition Induced Allylic Alkylation of Allenoates

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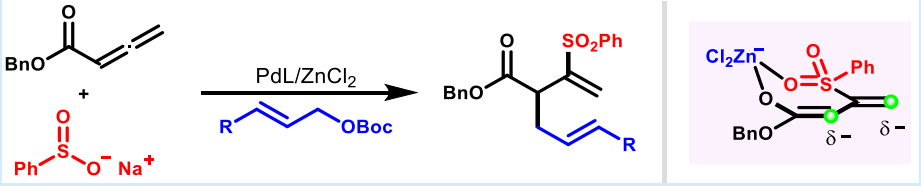
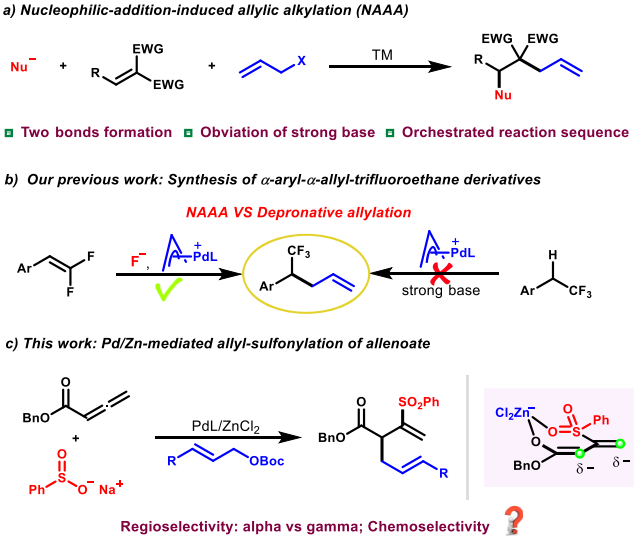
Supporting Information



ABSTRACT: A strategically novel Pd-catalyzed nucleophilic addition induced allylic alkylation reaction (NAAA) of allenoates has been successfully accomplished. By judiciously integrating $ZnCl_2$-promoted Michael addition with Pd-catalyzed allylic alkylation, allenoates readily undergo allyl-sunfonylation at the internal double bond, thus providing a straightforward avenue for the rapid assembly of a host of structurally diversified α-allyl-β-sufonylbut-3-enoate derivatives. The success of this transformation profits from a delicate control of the reaction kinetic of each elementary step, thanks to the synergistic interaction of Pd/Zn bimetallic system, thus suppressing either direct allylic sulfonylation or premature quenching of therein in situ generated ester enolate intermediate. Furthermore, by expanding the scope of workable Michael acceptor beyond those previously required doubly activated ones, such as methylenemalononitrile, the present work substantially enriches the repertoire of NAAA reactions.

Transition-metal-catalyzed allylic alkylations (AA) represent one of the most important techniques for carbon−carbon or carbon−heteroatom bond constructions and have therefore found wide applications in the synthesis of natural products and biologically relevant molecules.[1] Within this territory, while the past several decades have witnessed a tremendous evolvement, the majority of chemists' endeavors were focused either on the exploitation of diverse potentially applicable pro-nucleophiles[2] or on identifying more earth-abundant transition-metal catalysts capable of offering comparable or complementary reaction outcomes.[3,10] Furthermore, the traditional AA reaction in its own right is not without limitations. For example, while soft nucleophiles engaged AA reactions have been well explored,[2] the hard ones, however, remain much more recalcitrant,[4] and in the case of handling active nucleophile with comparatively low kinetic stability, such as a carbanion with a β-substituted leaving group, the reaction outcome always proves to be elusive. In this environment, the development of new strategies, which could ameliorate the existing issues, have been continuingly attracting considerable attention from the synthetic community. In this light, nucleophilic addition induced allylic alkylation (NAAA, Scheme 1a), which targets the functionalization of the nascent nucleophile resulting from Michael-type addition, emerges as an appealing alternative because of the following advantages: (i) it allows the generation of more than one bond in every catalytic cycle, which enables a more step-economical manifold for the rapid assembly of molecular complexity; (ii) strong base which is frequently employed in depronative allylation protocols could be omitted, which is deemed to be highly desirable in consideration of functionality tolerance; (iii) for kinetic reasons, the labile carbanion intermediate (such

Scheme 1. Development of Nucleophilic Addition Induced Allylic Alkylation Reactions



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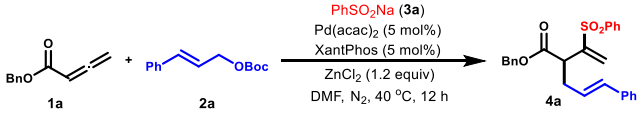
as α-CF_3-substituted benzylic anion), which would degrade via retro-Michael pathway in conventional deprotonative manner, could be functionalized through a Michael addition−allylic alkylation cascade (Scheme 1b).[5]

Notwithstanding the above-mentioned merits, the rational design of novel NAAA protocols is nontrivial because of the daunting challenge in identifying appropriate reaction components for the well-organized reaction sequence while suppressing the competing premature allylation of the pro-nucleophile as well as protonation of the post-nucleophile. In this context, elegant contributions from the groups of Yamamoto,[6] Stoltz,[7] Aggarwal,[8] Hou,[9] and Plietker[10] nicely show the potential of NAAA in the expedient construction of molecular complexity, although doubly activated Michael acceptors are always required for guaranteeing reaction selectivity from kinetic and thermodynamic considerations. Leveraging upon the NAAA strategy, our group has recently reported a novel synthetic method for the rapid access of α-aryl-α-allyltrifluoroethane derivatives.[5] It is worth pointing out that the conventional deprotonative allylation protocol turned out to be fruitless in this regard because of the number of overwhelming retro-Michael side reactions (Scheme 1b). While notable advances regarding NAAA have been obtained during the past two decades, there still remain massive shortcomings because of its heavy reliance on the use of doubly activated Michael acceptors or specific starting materials, which would more or less detract from its more broad applications in organic synthesis. Therefore, the development of novel protocols that allows the engagement of more readily available reaction components is still in high demand, practicably and theoretically.

Taking into account the reaction mechanism, the feasibility of a three-component NAAA reaction is envisioned to be founded on either of the following premises: (i) for the pro-nucleophile, the initiating Michael addition should be kinetically favored compared to the background allylation; (ii) the allylmetallic complex would undergo a reversible reaction with the pro-nucleophile while irreversibly interacting with the post-nucleophile. As part of our continuing interest in the development of new NAAA reactions, sulfinates draw our attention, assuming that they constitute a class of competent nucleophiles for Michael type addition[11] or substitution reactions as well as display medicinal importance of sulfone-derived architectures.[12] Furthermore, transition-metal-catalyzed C−S bond functionalization of sulfone was also actively pursued, with representative works from the groups of Trost,[13b] Li,[13c] Carretero,[13d] Crudden,[13e] Yoshikawa,[13f] Willis,[13g,h] and Baran[13i] underlying the potential applicability of sulfone as a new type of electrophile in cross-coupling reactions. Herein, we report a conceptually novel palladium-catalyzed allyl-sulfonylation of allenoate through a sulfinate-engaged NAAA reaction (Scheme 1c).

At the outset, the model reaction between benzyl buta-2, 3-dienoate **1a**, *tert*-butyl cinnamyl carbonate **2a**, and sodium benzenesulfinate **3a** was examined, and the representative results are compiled in Table 1. After systematic examination of all reaction parameters, the optimized reaction conditions were finally identified as follows: under the protection of N_2 atmosphere, a DMF solution of **1a** (2 equiv), **2a** (1 equiv), and **3a** (2 equiv) with $Pd(acac)_2$ (5 mmol %), XantPhos (5 mol %), and $ZnCl_2$ (1.2 equiv) as the catalyst, ancillary ligand, and Lewis acid, respectively, was heated at 40 °C for 12 h (entry 1, see the Supporting Information for details). Lewis acid additive

Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield[b] (%)
1	none	84[c]
2	$Mg(ClO_4)_2$ instead of $ZnCl_2$	22
3	without $ZnCl_2$	0
4	DPPF instead of XantPhos	18
5	MePhos instead of XantPhos	trace
6	DMA as solvent	73
7	DMSO as solvent	30
8	NMP as solvent	65
9	no $Pd(acac)_2$ or no XantPhos	0

[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), $PhSO_2Na$ (0.2 mmol), $ZnCl_2$ (0.12 mmol), $Pd(acac)_2$ (0.005 mmol), XantPhos (0.005 mmol) in DMF (1.0 mL) at 40 °C for 12 h. [b]NMR yield determined with 3,4,5-trimethoxybenzaldehyde as the internal standard. [c]Isolated yield.

played a crucial role in this transformation, with $ZnCl_2$ being the optimal choice. Whereas replacement of $ZnCl_2$ by $Mg(ClO_4)_2$ resulted in a significant decline in the yield of **4a** (entry 2), the omission of Lewis acid additive led to essentially no desired product formation (entry 3). It is therefore reasonable to assume that $ZnCl_2$ activates allenoate **1a** and in turn facilitates the assembly of post-nucleophile intermediate, probably as a seven-membered-ring structure.[2e,m,n] In addition, the ancillary ligands were found to be of vital importance for the success of this reaction, among which XantPhos showed the best performance (entries 1, 4, and 5). Other polar nonprotic solvents such as DMA, DMSO, and NMP all proved to be inferior to DMF in terms of reaction efficiency (entries 6−8). Further control experiments indicated the indispensability of both the palladium catalyst and the phosphine ligand, with no desired product obtained (entry 9).

With the optimized reaction conditions in hand, the scope of the reaction was subsequently investigated, and the results are summarized in Table 2. Initially, a collection of electronically different benzyl allenoate derivatives was examined, thus showing a nice tolerance of diverse functionalities in this transformation. For example, benzyl allenoate derivatives with electron-donating groups such as methyl and methoxy afforded the desired products in good yields (**4b**, **4c**). Halogen atoms such as F and Cl were tolerated (**4d**, **4e**). Electron-withdrawing substituents such as ester, trifluoromethyl, nitro, and nitrile groups also turned out to be well compatible with these reaction conditions (**4f**−**4i**). Pleasingly, benzyl allenoate substrate with an *o*-vinyl substituent was found to participate in this reaction smoothly, delivering the desired product **4j** in 81% yield. Furthermore, ethyl allenoate could be readily transformed into the desired product **4k**, albeit in somewhat attenuated reaction efficiency. Unfortunately, allenoates with an additional substituent at the 1- or 3-position failed to afford the desired products (see the Supporting Information for details). Subsequently, the reaction generality with respect to allyl carbonate was explored. The employment of *tert*-butyl (1-phenylallyl) carbonate as the reaction partner led to the formation of desired product **4a** in 65% yield, which unequivocally implicates the engagement of allylpalladium intermediate in this transformation. With respect to aromatic

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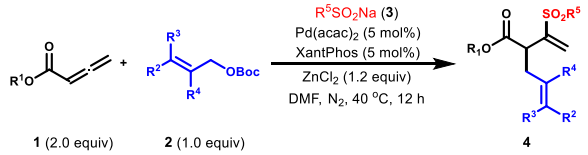
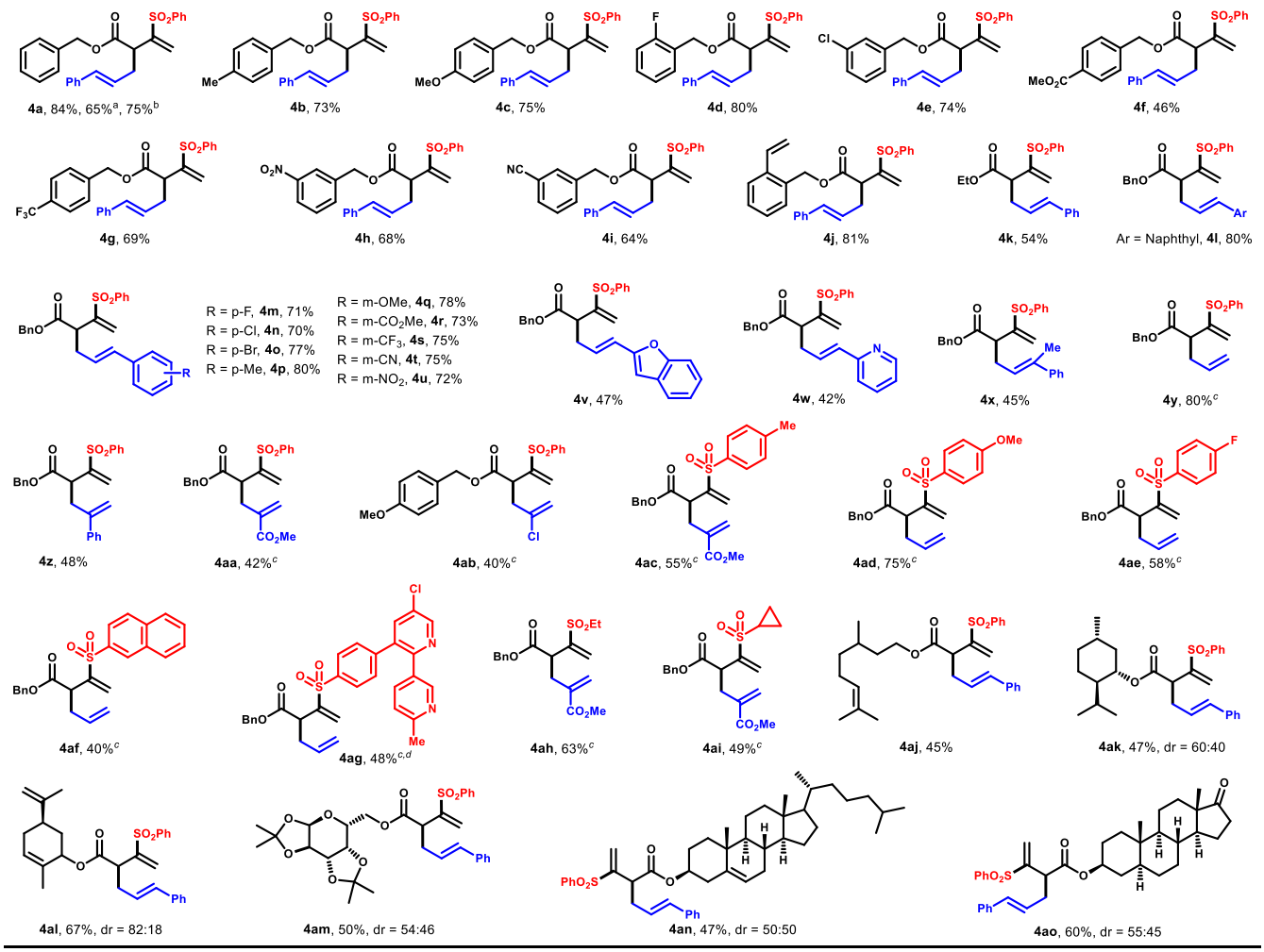
Table 2. Reaction Scope of Sufinate-Engaged NAAA Reaction of Allenoates





[a]Reaction using *tert*-butyl (1-phenylallyl) carbonate as the substrate. [b]Gram-scale reaction. [c]DtBPF (0.005 mmol) was used as the ligand. [d]Potassium sulfinate substrate was employed.

allyl carbonate examined, the electronic effect of decorating substituents was revealed to be inconsequential to this reaction, and the desired products with a diverse range of substituents such as halogen, alkyl, alkoxyl, ester, trifluoromethyl, nitrile, and nitro groups were obtained in good yields (**4m**−**4u**). Expectedly, naphthyl-derived allyl carbonate underwent this transformation without any difficulty and provided the desired product **4l** in 80% yield. It also needs to be pointed out that allyl carbonates derived from heteroarenes were also viable substrates as represented by the cases of **4v** and **4w**. To our delight, trisubstituted allyl carbonate derivatives also reacted uneventfully, as showcased by the example of **4x**. While examining the reaction generality of allyl carbonate, we were quite surprised to find that the simplest allyl carbonate was inapplicable to the standard reaction conditions. Further refinement of the reaction parameter ultimately led to the formation of the desired product **4y** in 80% yield when DtBPF was substituted for XantPhos as the assisting ligand. Interestingly, while 2-phenyl-substituted allyl carbonate was accommodated by the XantPhos-based protocol, substrates with 2-CO_2Me and 2-Cl substituents, on the contrary, only generated the desired products when DtBPF was used as ligand (**4z**, **4aa**, **4ab**). The exact reason for such a discrepancy is not clear at the present stage. Because of the medicinal importance of sulfonylated framworks, the reaction generality of sulfinate was also interrogated. Aryl sulfinates containing substituents such as Me, OMe, and F afforded the desired products in moderate to good yields (**4ac**−**4ae**). In the case of using 2-naphthyl sulfinate, the desired product **4af** could be obtained in 40% yield. Delightfully, the reaction was not restricted to aryl sulfinates, and alkyl sulfinates, irrespective of being linear or cyclic, were tolerated (**4ah**, **4ai**). Notably, when potassium sulfinate derived from etoricoxib was employed, the reaction occurred smoothly and the desired product **4ag** was

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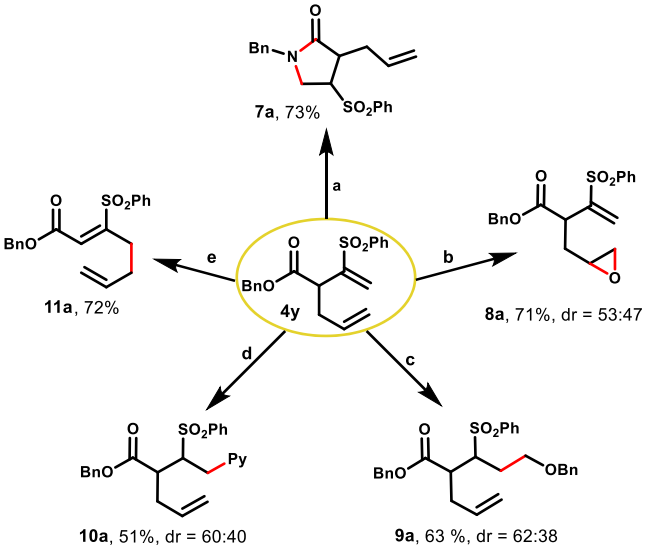
isolated in 48% yield. To further challenge the synthetic applicability of this reaction, allenoates derived from a collection of naturally occurring molecules were tested, and the desired products were all obtained in synthetically useful yields, thus indicating the generality of this method for the synthetic elaboration of complex architectures (**4aj**−**4ao**). Also of note, a gram-scale reaction of the model reaction led to the generation of product **4a** in 75% yield (1.46 g), which in turn underscores the practicality of the present transformation.[14,15]

To gain more insight into the exact role of Pd/Zn bimetallic composition in this reaction, control experiments with the omission either ingredient were initially carried out (Scheme 2). It was found that the model reaction carried out in the

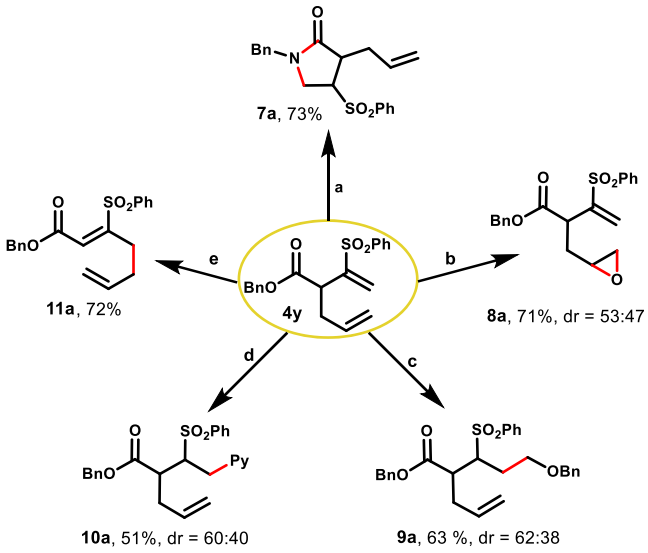
Scheme 2. Control Experiments



absence of $ZnCl_2$ exclusively afforded the allylic sulfonylation byproduct **5a**, while the omission of Pd catalyst led to the formation of only Michael addition products **6a**/**6a′**, with protonation of in situ formed ester enolate on the α- and γ-position, respectively.[16] Collectively, these results could be interpreted by assuming that (i) zinc salt could selectively activate allenoate **1a**, thus making the sulfinate-based Michael addition kinetically much more favored compared with the background allyic sulfonylation reaction, and (ii) the palladium catalyst on the other hand engages allyl carbonate with ease to generate allylpalladium intermediate; the regioselectivity for the enolate allylation is believed to be controlled globally by electronic and steric effects. Subsequently, to differentiate the working modes that we assumed as the premise for the success of this three-component NAAA reaction, further control experiments with **5a** and **6a** were examined. When the reaction of **1a** and **5a** was subjected to the standard reaction conditions, essentially no desired product **4a** was obtained, which firmly rules out the reversibility of allylic sulfonylation process and also the intermediacy of **5a** in the whole transformation. In addition, when we added **6a** to the reaction carried out between **1c** and **2a**, both allylation products **4a** and **4c** were obtained. It follows that the success of this reaction is attributed to the kinetically favored Michael addition associated with irreversible enolate allylation by virtue of the integrated effects of Pd/$ZnCl_2$ bimetallic system.

To showcase the utility of the obtained α-allyl-β-sufonylbut-3-enoate derivatives, the synthetic transformation of **4y** was subsequently launched (Scheme 3). The treatment of **4y** with

Scheme 3. Synthetic Transformation Conditions[a]



[a]Key: (a) $BnNH_2$, MeOH, 65 °C, 24 h; (b) *m*-CPBA, DCM, 0 °C to rt, 42 h; (c) $Ir[(dF)(CF_3)(ppy)_2(dttbpy)](PF_6)$, benzyloxyacetic acid, Cs_2CO_3, DMF, rt, 96 h,15 W blue LED; (d) $Ir(ppy)_2(dttbpy)(PF_6)$, 2-bromopyridine, HEH, H_2O/DMSO, rt, 12 h, 15 W blue LED; (e) PhCl, 160 °C, 12 h.

benzylamine allows a smooth generation of pyrrolidin-2-one product **7a** in 73% yield,[17] and the *m*-CPBA-mediated epoxidation selectively occurred on the more electron-rich double bond to deliver product **8a** in 71% yield.[18] In addition, while the present reaction is not applicable to γ-substituted allenoates, the Giese reaction, to some extent, provides a pathway by enabling an expedient introduction of either aryl or alkyl groups to the γ-position (**9a**, **10a**).[19,20] Finally, hepta-2,6-dienoate product **11a** could be readily obtained through Cope rearrangement from **4y**.

In summary, by making use of sulfinates, allyl carbonates as pro-nucleophiles, and allyl donors, respectively, a regioselective NAAA reaction of a wide spectrum of structurally diversified allenoates was developed. The employment of the Pd/Zn bimetallic reaction system is believed to be the key point for suppressing the competing background side reactions, thus enabling a well-organized cascade elaborations. Furthermore, the amenability of allenoate derivatives in this transformation not only allows the generation of molecular framework in high complexity but more importantly greatly expands the compatibility of NAAA type reaction beyond those often required doubly activated Michael acceptors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02728.

Experiemental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(15) In order to achieve asymmetric allylic alkylation, chiral Zn-based complexes were examined in the reaction, resulting in either no desired product formation or no enantioselectivity. See the Supporting Information for details. For the selected examples of chiral Zn-complex-engaged asymmetric allylic alkylation reactions, see: (a) Huo, X.; He, R.; Zhang, X.; Zhang, W. *J. Am. Chem. Soc.* **2016**, *138*, 11093. (b) He, R.; Liu, P.; Huo, X.; Zhang, W. *Org. Lett.* **2017**, *19*, 5513.

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