Enantioselective Synthesis of Skipped Dienes via Iridium-Catalyzed Allylic Alkylation of Phosphonate Carbanions

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Abstract: An enantioselective synthesis of skipped diene has been developed based on an iridium-catalyzed allylic alkylation of phosphonate carbanions and Horner-Wadsworth-Emmons olefination. This two-step protocol benefits from the ease of accessibility of the starting materials and delivers C2-substituted skipped dienes, bearing a C3 stereogenic center, in moderate to excellent yields and generally with outstanding enantioselectivities. This is the first catalytic enantioselective allylic alkylation of phosphonate carbanions.

Dienes containing an intervening sp^3 carbon center between the two olefins, commonly known as skipped dienes, are found in a plethora of natural products, including primary fatty acid metabolites and alkaloids.[1] The presence of a stereogenic center between two non-conjugated olefin functionalities in such naturally occurring compounds (Figure 1) have inspired the development of new strategies for the *de novo* synthesis of skipped dienes. Strategies for the construction of 1,4-diene motifs mainly comprise of enyne coupling,[2] hydrovinylation of alkene[3] and allylic substitution reactions.[4]

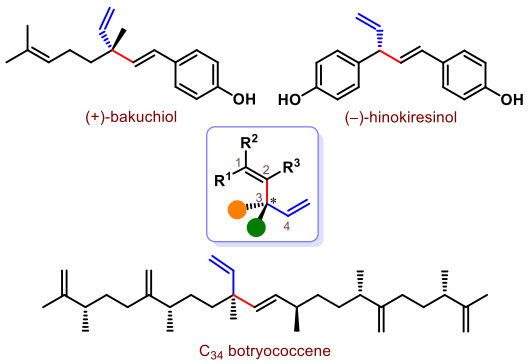
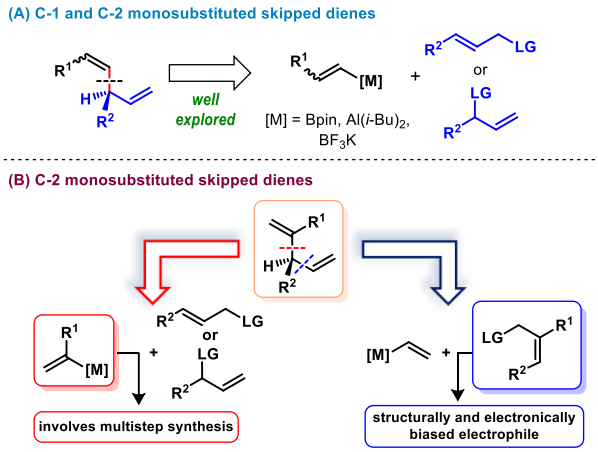


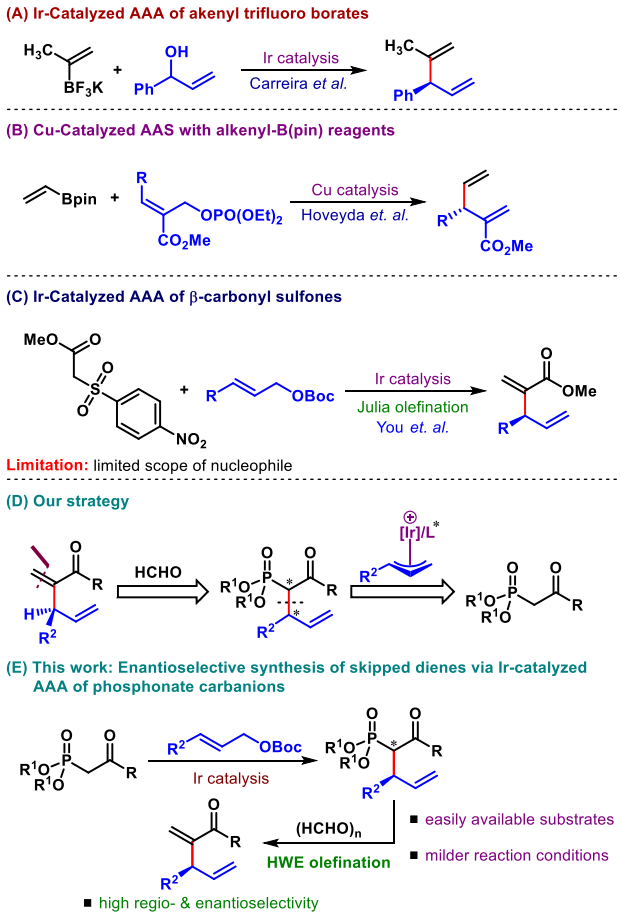
Figure 1. Natural products containing skipped dienes

Over the past decade, transition metal catalyzed asymmetric allylic substitution (AAS) involving alkenyl boron and aluminum reagents have gained immense popularity for the formation of diversely functionalized skipped dienes (Scheme 1A).[4] Notwithstanding the phenomenal advancement in this field, difficulties associated with the preparation of preformed vinyl nucleophiles as well as electronically and structurally biased electrophiles curbed the potential of the aforesaid protocol to a great extent (Scheme 1B). Amidst the 1,4-diene motifs, C2 disubstituted skipped dienes having a chiral center at C3 represents an interesting moiety. Due to the limitations concerning the prevalent AAS methodologies, development of new strategies for the synthesis of such unique structures is desirable. In this regard, Carreira group successfully achieved Ir-catalyzed asymmetric allylic alkylation (AAA) of potassium trifluoro(2-propenyl) borates (Scheme 2A).[4c] Although NHC-Cu-catalyzed enantioselective coupling of alkenyl borates and allylic phosphates developed by Hoveyda *et al.* afforded structurally similar skipped dienes, it involved the use of electronically biased electrophiles (Scheme 2B).[4b] A simple two step protocol for the generation of C2 disubstituted skipped dienes, comprising of Ir-catalyzed AAA of β-carbonyl sulfones and a subsequent Julia olefination, was realized by the You group in 2012.[4d] However, the scope of this reaction was limited only to α-allylic methyl acrylates (Scheme 2C).



Scheme 1: Strategies for the Synthesis of Skipped Dienes by Transition Metal-Catalyzed Asymmetric Allylic Alkylation

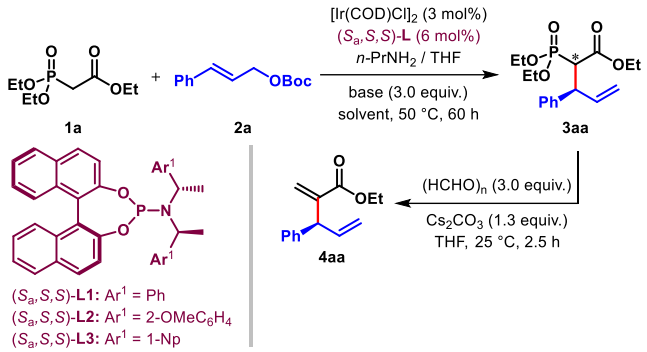
We envisioned that Ir-catalyzed allylic alkylation of phosphonoacetates followed by a sequential Horner-Wadsworth-Emmons (HWE) olefination would install a stereocenter at the C3 position of C2-disubstituted skipped dienes (Scheme 2D). Ever since the seminal report by Takeuchi[5] and Helmchen[6] in 1997, a wide variety of stabilized enolates and enolate equivalents generated from active methylene compounds have been explored in Ir-catalyzed allylic alkylation reactions.[7] Surprisingly, structurally analogous phosphonoacetates have never been utilized as a nucleophile in Ir-catalyzed AAA. With our interest in Ir-catalyzed AAS reactions,[8] we sensed this as an opportunity for developing a two-step protocol for the synthesis of skipped dienes *via* the intermediacy of α-allylic phosphonoacetate (Scheme 2E).



Scheme 2. Previous Reports for the Enantioselective Synthesis of C-2 Disubstituted Skipped Dienes

We began our investigation with the goal of identifying a suitable catalyst and compatible reaction conditions for the model reaction between triethyl phosphonoacetate **1a** with *tert*-butyl cinnamyl carbonate **2a** in THF at 60 °C. Using 6 mol% of an *in situ* generated complex derived from $[Ir(COD)Cl]_2$ and Feringa's phosphoramidite ligand (S_a,*S*,*S*)-**L1**, in the presence of 2.0 equiv of NaH, the desired α-allylic phosphonoacetate **3aa** was formed exclusively as a branched isomer in 35% yield. The poor diastereoselectivity (1:1 dr) observed in this allylic alkylation reaction was assumed to be arising due to the presence of an acidic α-proton in phosphonoacetate and deemed to be inconsequential under our synthetic strategy. Accordingly, the diastereomeric mixture of **3aa**, when subjected to HWE olefination with formalin in the presence of Cs_2CO_3, resulted in skipped diene **4aa** with 98:2 er (Table 1, entry 1). Screening of bases for the allylic alkylation reaction revealed KO*t*-Bu to be the optimum (entry 3). Increasing the amount of the nucleophile **1a** as well as the base and a reduction in reaction temperature to 50 °C improved the yield of the AAA step considerably (entry 4). With the objective of carrying out this two-step sequence in a one-pot manner, the HWE olefination step was attempted with KO*t*-Bu as the base. Although the skipped diene **4aa** was obtained with comparable yield, the enantioselectivity of the overall process dropped noticeably (entry 4). However, a combination of Cs_2CO_3 and paraformaldehyde delivered **4aa** in improved yield without compromising the enantiopurity (entry 5). The reaction medium turned out to be crucial for the AAA reaction and CH_2Cl_2 was found to be the best, while THF remained as a solvent of choice for the olefination step. Other ligands (**L2**-**L3**) were also examined for the AAA reaction. The use of Alexakis' ligand **L2** improved both the yield and the enantioselectivity of the allylic alkylation step, as the skipped diene **4aa** was isolated in an overall yield of 75% with 99:1 er (entry 8).

Table 1. Optimization of Reaction Parameters[a]



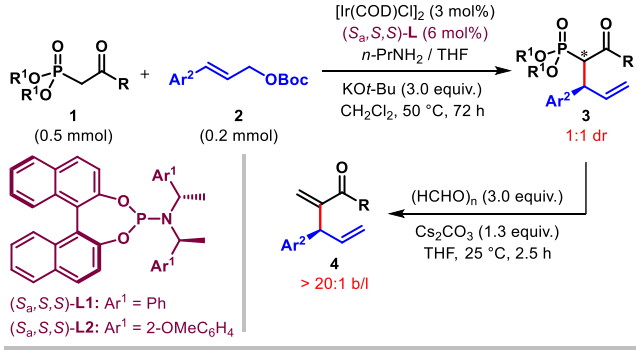
Entry	2a/1a	base	solvent	yield (%) 3aa[b]	yield (%) 4aa[c]	er of 4aa
1[d,e]	1:2	NaH	THF	35	29	98:2
2[d]	1:2	Cs_2CO_3	THF	<5	—	—
3[d,e,f]	1:2	KO*t*-Bu	THF	62	50	97.5:2.5
4[g]	1:2.5	KO*t*-Bu	THF	71	55	96:4
5	1:2.5	KO*t*-Bu	CH_2Cl_2	71	65	98:2
6	1:2.5	KO*t*-Bu	$CHCl_3$	<5	—	—
7	1:2.5	KO*t*-Bu	PhMe	60	—	—
8[h,i]	**1:2.5**	**KO*t*-Bu**	**CH_2Cl_2**	**84**	**75**	**99:1**
9[j]	1:2.5	KO*t*-Bu	CH_2Cl_2	54	42	97:3

[a]Reactions were carried out on 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR spectroscopy with mesitylene as internal standard. [c]Yield of the isolated product over two-steps after chromatographic purification. [d]Reaction was carried out at 60 °C for 48 h with 2.0 equiv. of base. [e]Formalin was used in the second step. [f]Second step was carried for 24 h with 3.0 equiv. of Cs_2CO_3. [g]KO*t*-Bu was used as a base in the second step. [h](S_a,*S*,*S*)-**L2** was used. [i]Reaction carried on 0.2 mmol scale. [j](S_a,*S*,*S*)-**L3** was used.

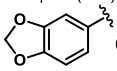
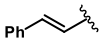
Having identified the optimum reaction conditions (Table 1, entry 8), we chose to demonstrate the generality of this two-step protocol with other substrate combinations for the enantioselective synthesis of α-allylic acrylates. As shown in Table 2A, triethyl phosphonoacetate **1a** underwent facile reaction with a wide variety of allylic *tert*-butyl carbonates **2**. Cinnamyl carbonates bearing electron donating groups either on the *para* or *meta*-position of the phenyl ring (**2b**-**g**) furnished the

skipped dienes **4ab**-**ag** with good to high yields and uniformly high level of enantioselectivities (entries 2-7). Cinnamyl carbonate derivatives bearing electron-deficient arene ring (**2h**-**j**) also fared well under our reaction conditions (entries 8-10). Against the usual trend of the catalyst system employed herein, *ortho*-methoxy cinnamyl carbonate **2k** reacted smoothly to afford the desired product in decent yield and with good enantioselectivity (entry 11). However, the deleterious effect of the *ortho*-substitution was obvious from the comparative outcome of the reactions with the two isomeric dichloro-substituted cinnamyl carbonates **2l** and **2m** (entries 12-13). Along the same line, 1-napthyl-substituted allylic carbonate **2n** turned out to be an inferior substrate for this reaction compared to its 2-napthyl counterpart **2o** (entries 14-15). The scope of this protocol is not restricted to cinnamyl carbonates. Allylic carbonates bearing heterocyclic (**2p**-**q**) as well as alkenyl substituents (**2r**) delivered the corresponding skipped dienes in moderate to high yields with excellent er. Unfortunately, skipped dienes with aliphatic substituents could not be synthesized using this two-step protocol: While the AAA reaction was found to be facile, the corresponding α-allylic phosphonoacetates bearing aliphatic substituents resulted in a complex mixture under HWE olefination conditions.

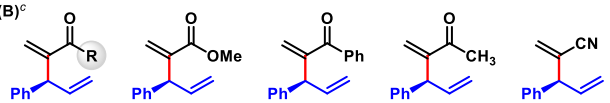
Table 2. Scope of Asymmetric Allylic Alkylation of Phosphonates[a]



(A)

entry	Ar^2 (**4**)	yield (%)	er
1	Ph (**4aa**)	75	99:1
2	4-MeC_6H_4 (**4ab**)	89	99:1
3	4-$OMeC_6H_4$ (**4ac**)	83	99:1
4	4-FC_6H_4 (**4ad**)	72	99:1
5	4-ClC_6H_4 (**4ae**)	70	99:1
6	4-BrC_6H_4 (**4af**)	71	99:1
7	3-MeC_6H_4 (**4ag**)	70	99:1
8	4-$CF_3C_6H_4$ (**4ah**)	62	n.d.
9	3-BrC_6H_4 (**4ai**)	78	99:1
10	3-FC_6H_4 (**4aj**)	55	98.5:1.5
11	2-$OMeC_6H_4$ (**4ak**)	60	96:4
12[b]	3,4-$Cl_2C_6H_3$ (**4al**)	63	99:1
13[b,c]	2,4-$Cl_2C_6H_3$ (**4am**)	42	75:25
14	1-Naphth (**4an**)	45	83:17
15	2-Naphth (**4ao**)	91	99:1
16	 (**4ap**)	81	99.5:0.5
17	2-Thienyl (**4aq**)	65	99:1
18	 (**4ar**)	52	

(B)[c]



4ba[a] 37% yield 96.5:3.5 er; **4ca** 75% yield 99:1 er; **4da** 70% yield 98.5:1.5 er; **4ea** 59% yield 98.5:1.5 er

[a]Unless noted otherwise, the reaction conditions indicated above were followed. Yields refer to the isolated product over two-steps after chromatographic purification. Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase. [b]The er was determined by reducing the ester group to alchohol. [c]**L2** was used as ligand.

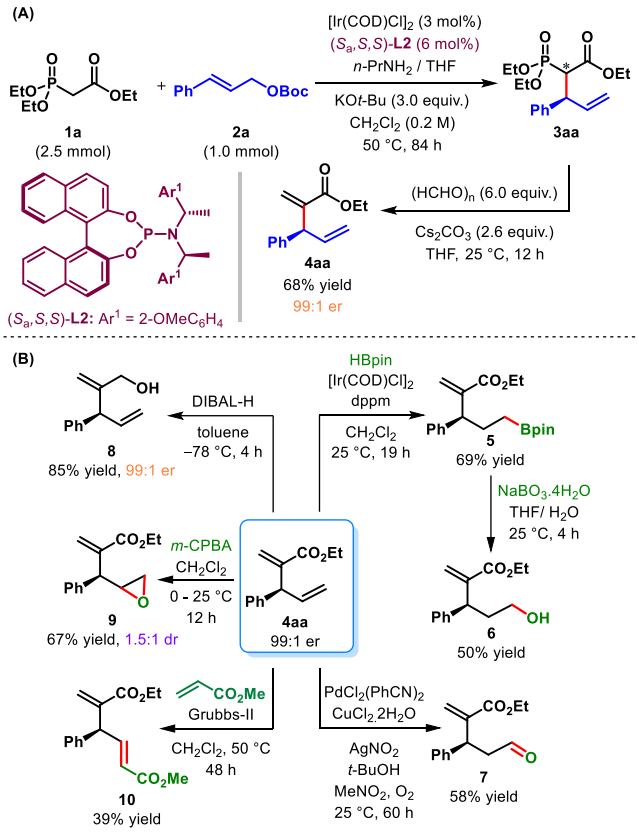
After exhibiting the scope and limitations with respect to the allylic carbonates, we examined the reactivity of other phosphonate derivatives (Table-2B). Apart from phosphonoacetates, phosphonates bearing other electron-deficient functionalities such as ketone (**1c**-**d**) and nitrile (**1e**) were well tolerated under the standard reaction conditions and generated the respective skipped dienes **4ca**-**ea** in moderate to good yields with high enantioselectivities.

To determine the stereochemistry of the skipped dienes, α-allylic methyl acrylate **4ba** was synthesized following our two-step protocol. The absolute configuration of **4ba** was ascertained by comparing its specific rotation with that reported in the literature.[4c,d] The absolute stereochemistry of other skipped dienes shown in Table 2 was assigned as the same by analogy.

To showcase the scalability of our protocol, the reaction between **1a** and **2a** was carried out on a 1.0 mmol scale (Scheme 3A) under our standard reaction conditions. Despite a little longer reaction time, the skipped diene **4aa** was isolated in a yield comparable to the smaller scale reaction (Table 2, entry 1) with the same level of enantioselectivity.

This two-step protocol represents a formal enantioselective α-allylic alkylation of α,β-unsaturated carbonyls and nitriles – a transformation challenging in itself and with only a few solutions at hand. Having access to these α-allylic α,β-unsaturated carbonyls, we decided to elaborate these compounds to related synthetic building blocks.

Ir-Catalyzed hydroboration took place selectively on the electron rich terminal double bond of **4aa** and afforded the alkyl borate **5** in 69% yield.[9] Oxidation of **5**, afforded the overall anti-Markovnikov hydration product **6**, albeit in modest yield. Aldehyde-selective Wacker oxidation was also found to be selective to electron rich olefin and produced the aldehyde **7** in 58% yield. Reduction of the ester group of **4aa** to primary alcohol, was possible at lower temperature and afforded the allylic alcohol **8** in high yield. Epoxidation of **4aa** with *m*-CPBA, although proceeded smoothly, the corresponding epoxide (**9**) was isolated with only 1.5:1 dr. Olefin cross metathesis of **4aa** with methyl acrylate in the presence of Grubbs second generation catalyst delivered **10**, comprising of two different α,β-unsaturated ester functionalities.



Scheme 3. (A) Scale-up Synthesis and (B) Synthetic Elaboration of Skipped Diene 4aa

In summary, we have developed the first catalytic enantioselective allylic alkylation of phosphonate carbanions for the synthesis of skipped dienes. This Ir-catalyzed highly enantioselective allylic alkylation is followed by Horner-Wadsworth-Emmons reaction with formaldehyde. This two-step approach benefits from the easily available starting materials as well

as mild reaction conditions. The skipped dienes were synthesized exclusively in a branched selective manner in moderate to high yields and generally with excellent enantioselectivities.

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