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Chiral-Anion-Mediated Asymmetric Heck–Matsuda Reaction of Acyclic Alkenyl Alcohols

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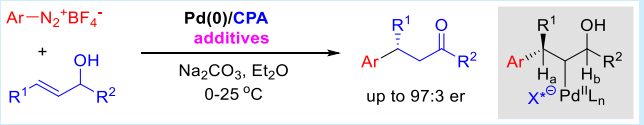
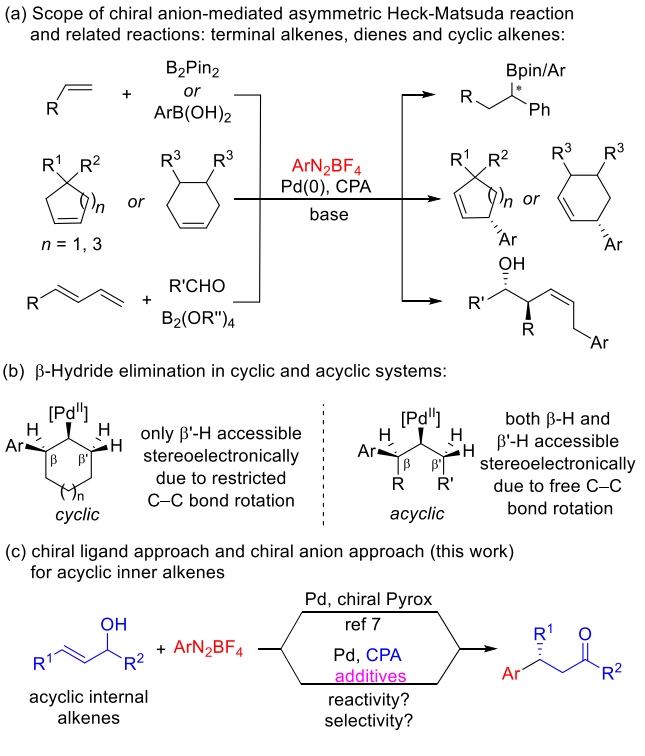
ABSTRACT: Acyclic internal alkenes are a class of challenging substrates in asymmetric Heck-type reactions due to difficulties related to both reactivity and selectivity control. Employing acyclic alkenyl alcohols, an asymmetric Heck–Matsuda reaction is developed through the strategy of chiral anion phase transfer. Various chiral ketones could be obtained in high levels of enantioselectivity. A catalytic amount of dimethyl sulfoxide (DMSO) as an additive is crucial for the reaction to suppress the palladium-hydride-mediated side reactions.



The Heck–Matsuda arylation reaction,[1] utilizing more reactive aryl diazonium salts readily prepared from corresponding anilines,[2] exhibits remarkable advantages over traditional cross-coupling chemistry.[3] Due to the feasibility for oxidative addition of the diazonium salts, oxidation-sensitive electron-rich ligands are not required, and the reactions can typically be performed under mild conditions without strict exclusion of oxygen.[4] On the other hand, the enantioselective variants of the Heck–Matsuda reaction are more challenging largely because of the incompatibility between common phosphine-based ligands and diazonium salts.[5] One strategy to overcome this challenge is applying nitrogen-based chiral ligands, as successfully demonstrated by the groups of Correia[6] and Sigman.[7] More specifically, Correia's group has reported a series of desymmetric Heck–Matsuda arylations of cyclic and acyclic olefins using chiral bisoxazolines, while Sigman's group has developed enantioselective arylations of acyclic alkenyl alcohols utilizing chiral pyridine oxazolines.

As an alternative approach, Toste's group first discovered that chiral anion phase-transfer (CAPT) catalysis could successfully enable related processes.[8−10] Toste and co-workers have reported enantioselective 1,1-arylborylation,[9a] 1,1-diarylation,[9g] and Heck–Matsuda arylation of alkenes.[9h,i] Our group also established an asymmetric multicomponent reaction of diazonium salts, diborates, aldehydes, and 1,3-dienes (Scheme 1a).[9j] Albeit that CAPT has proven to be a potent strategy in asymmetric Heck–Matsuda-type reactions, the scope of the reactions has been limited to terminal alkene and dienes and cyclic alkenes.[9a,g−j] To date, acyclic inner alkenes are still not applicable for the Matsuda-type reactions under CAPT conditions. In enantioselective intermolecular Heck-type reactions, cyclic alkenes are usually more preferable for the feasibility to control the selectivity of β-hydride elimination because of the conformational rigidity (Scheme 1b, left).[11] On the other hand, it is much more challenging to distinguish between similar C–H bonds in the β-hydride elimination event of acyclic sterically and electronically nonbiased internal

Scheme 1. Chiral-Anion-Mediated Asymmetric Heck–Matsuda Reaction and Related Reactions with Terminal Alkenes, Dienes, and Cyclic Alkenes



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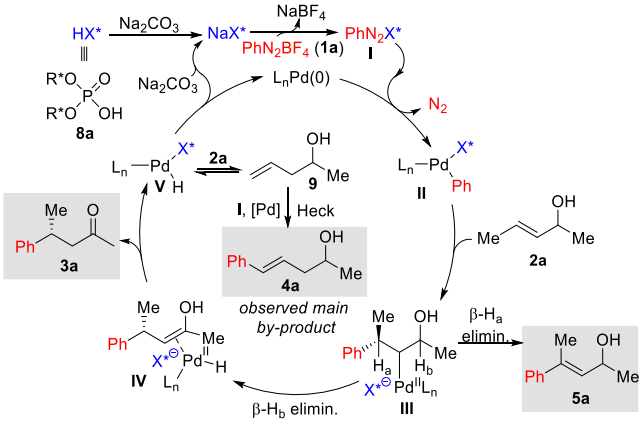
alkenes (Scheme 1b, right).[7,12] Although these issues have been overcome through rational design of ligands by Sigman's group and others,[6,7,13] it still remains unclear and challenging under CAPT conditions, where the regioselectivity of the β-hydride elimination as well as the migratory insertion mainly relies on the chiral counteranion. Further, since the unactivated acyclic internal alkenes generally exhibit lower reactivity in Heck-type reactions compared to terminal and cyclic alkenes, it is still questionable if sufficient reactivity could be achieved in the CAPT catalysis scenario for these substrates. Despite these challenges, to extend the application scenarios of CAPT, herein, we report our efforts on the investigation of the chiral-anion-mediated asymmetric Heck–Matsuda reaction of acyclic alkenyl alcohols (Scheme 1c).

The hypothesized chiral-anion-mediated asymmetric Heck–Matsuda reaction is outlined in Scheme 2 with phenyl

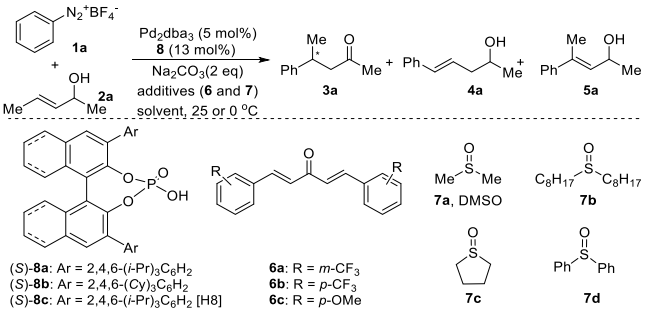
Scheme 2. Chiral Anion-Mediated Asymmetric Heck-Matsuda Reaction of Acyclic Alkenyl Alcohols



dazonium salt **1a** and allylic alcohol **2a** as the typical substrates and chiral phosphoric acid **8a** as the source of the chiral anion. In this strategy, insoluble diazonium salt is transferred into the solution phase to give ion-pair **I**[9a,g–j,10] via anion exchange with sodium phosphate generated from **8a** and sodium carbonate. The ion pair then undergoes oxidative addition by the Pd(0) species to give Pd(II) intermediate **II**[3,9b] with the chiral phosphate as the counteranion, which generates intermediate **III** after migratory insertion of alkene **2a**. In this stage, two possible β-H elimination processes are possible to form either byproduct **5a** or intermediate **IV**. It requires the chiral anion to govern the selectivity for a preferred β-H_b elimination process. Olefin dissociation and tautomerization of the enol afford the desired chiral ketone **3a** and Pd hydride species **V**, which then undergoes formal reductive elimination and regenerates Pd(0) and sodium phosphate as suggested by Toste and co-workers.[9h] On the other hand, the alkene isomerization issue has been previously observed in Heck–Matsuda reactions.[14,9h] In this case, terminal alkene **9** can be formed and undergoes another Heck reaction to produce byproduct **4a**.

To verify the feasibility of the hypothesized reaction, phenyldiazoniumtetrafluoroborate **1a** and (*E*)-pent-3-en-2-ol **2a** were subjected to 5 mol % of Pd_2dba_3 and 13 mol % of chiral phosphoric acid **8a** with Na_2CO_3 in ether (Table 1, entry 1). Encouragingly, the reaction did afford chiral ketone **3a** with moderate yield and excellent enantioselectivity. At the same time, a notable amount of compound **4a** was surprisingly

Table 1. Reaction Optimization[a]



entry	8	additives	solvent	yield (3a, %)[b]	er[c]	3a/4a[d]
1	8a	none	Et_2O	41	95:4	2.5:1
2	8a	none	MTBE	45	85.5:14,5	4:1
3	8a	none	THF	44	87.5:12.5	2.3:1
4	8a	none	DCM	trace	-	-
5	8a	6a	Et_2O	60	94:6	2.6:1
6	8a	6b	Et_2O	57	93.5:6.5	2.8:1
7	8a	6c	Et_2O	61	93.5:6.5	3:1
8	8a	6a, 7a	Et_2O	68	91:9	>20:1
9[e]	8a	6a, 7a	Et_2O	82	94.5:5.5	>20:1
10[e]	8a	6a, 7b	Et_2O	75	95:5	>20:1
11[e]	8a	6a, 7c	Et_2O	57	95:5	>20:1
12[e]	8a	6a, 7d	Et_2O	47	95:5	5:1
13[e]	8b	6a, 7a	Et_2O	75	87.5:12.5	>20:1
14[e]	8c	6a, 7a	Et_2O	82(75[f])	95:5	>20:1

[a]Unless noted otherwise, the reaction of **1a** (0.1 mmol) with **2a** (0.2 mmol) was carried out with Pd_2dba_3 (0.005 mmol), **8** (0.013 mmol), Na_2CO_3 (0.2 mmol), additive **6** (0 or 0.015 mmol), and additive **7** (0 or 0.016 mmol) in 2.0 mL of solvent at 25 °C for 12 h; a trace amount of **5a** was observed. [b]NMR yield. [c]Determined by HPLC analysis. [d]Determined by ^{1}H NMR analysis of the crude reaction mixture. [e]The reaction was carried out at 0 °C. [f]Isolation yield.

observed as the main byproduct, and only a trace amount of **5a** was detected. Employing methyl *tert*-butyl ether as the solvent to furnish the reaction provided the product with a slightly higher chemoselectivity, moderate yield, and lower enantioselectivity (entry 2). Switching the solvent to THF led to no better results, and the reaction turned completely unproductive when using DCM as reaction media (entries 3 and 4). Inspired by previous observations by Fairlamb,[15] Trost,[9a] and Sigman[13j] that dibenzylideneacetone (dba) derivatives can possibly stabilize palladium species along the catalytic cycle and thus affect the catalytic performance, several dibenzylideneacetone (dba) derivatives (**6a–6c**) were tested as additives for the reaction in ether (entries 5–7). It was found that in all these reactions a significant boost in the yield was observed but with lower enantioselectivity, and the generation of byproduct **4a** could not be surpressed (vs entry 1). To further optimize the reaction and inhibite the side reaction, we noticed that dimethyl sulfoxide (DMSO) was frequently used as the solvent or ligand for the palladium-catalyzed reaction.[16] Beller and co-workers found that DMSO as a cosolvent could tune the selectivity of the Heck arylation of cyclohexene with aryl bromides.[16g] It was found that the addition of 15 mol % DMSO (**7a**) in the reaction sufficiently suppressed the generation of **4a** and led to a slight increase in the yield, albeit that slightly lower enantioselectivity was obtained (entry 8 vs entry 5). Lowering the temperature to 0 °C rendered the reaction with 82% yield, excellent chemoselectivity, and a 94.5:5.5 er (entry 9). At this stage, due to the significant

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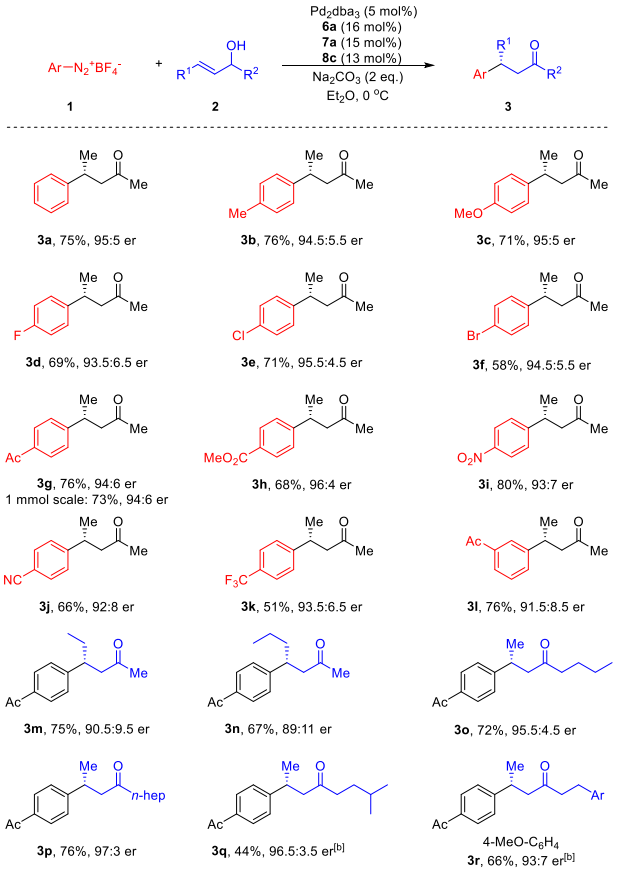
influence of DMSO, a series of sulfoxides (**7b**, **7c**) were examined, and DMSO **7a** was found to be the optimal additive (entries 10−12). Notably, while dialkyl sulfoxides **7b** and **7c** could also efficiently avoid the generation of **4a**, diaryl sulfoxide **7d** with lower coordination ability exhibited much less of an effect on surpressing the side reaction. Further, slightly enhanced enantioselectivity and yield could be obtained when 8H-BINOL-based phosphoric acid **8c** was used (entries 9 and 13 vs 14).

Under the optimized reaction conditions, we first explored the scope of aryl diazonium salts for the reactions with allylic alohol **2a** (Scheme 3). A broad scope of aryldiazonium salts

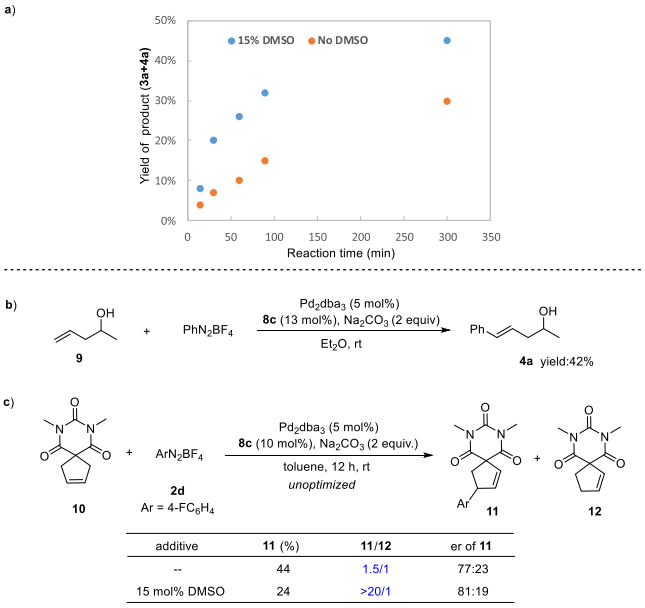
Scheme 3. Substrate Scope[a]



[a]Unless noted otherwise, the reaction of **1** (0.1 mmol) and **2** (0.2 mmol) was carried out with Pd_2dba_3 (0.005 mmol), **8c** (0.013 mmol), **6a** (0.016 mmol), **7a** (0.015 mmol), and Na_2CO_3 (0.2 mmol) in Et_2O (2.0 mL) at 0 °C for 12 h. [b]25 °C.

bearing 4-substitutuents, either electron-donating (**3b**, **3c**) or -withdrawing (**3d**−**3k**), could be well-tolerated, giving rise to the corresponding chiral ketone in 51 to 80% yield with good to excellent enantioselectivity (up to 96:4 er). Notably, a bromo substituent at the phenyl ring (**3f**) could remain unchanged during the Pd(0)-catalyzed reaction, probably due to the high reactivity toward oxidative addition of the diazonium group. A similar level of yield and enantioselectivity were observed when the reaction yielding **3g** was performed in a 1 mmol scale. Meta-substituted diazonium salts could also undergo the reaction smoothly, albeit with slightly lower enantioselectivity (**3l**). Ortho-substituted diazonium salts, e.g., 2-methylphenyl diazonium salt, were not ideal subtrates for the reaction due to lower reactivity, in accordance with previous reports. Next, various allyl alcohols were investigated for the reaction (**3m**−**3q**). Switching R^1 from a methyl to ethyl (**3m**) or *n*-propyl (**3n**) group also led to smooth reactions, providing the corresponding product with 90.5:9.5 and 89:11 er, respectively. On the other hand, when the R^2 group of the allylic alcohols was altered to other alkyl groups, e.g., *n*-butyl (**3o**), *n*-heptyl (**3p**), and isopentyl (**3q**), similar levels of yield and high to excellent enantioselectivities could be achieved. In the case of **3r**, when an allylic alcohol bearing an aryl group was employed, the desired product could also be obtained in moderate yield with high enantioselectivity.

To gain insight into the effect of DMSO in the reaction, the reaction processes with or without DMSO were monitored. Besides the effect to suppress the formation of byproduct **4a**, as shown in Figure 1a, the presence of a catalytic amount of



additive	**11** (%)	**11**/**12**	er of **11**
--	44	1.5/1	77:23
15 mol% DMSO	24	>20/1	81:19

Figure 1. DMSO effect in the reaction and control experiments.

DMSO also led to a considerable boost of the apparent reaction rate in the early stage (Table 1, entry 8 vs 5). Side product **4a** could indeed be isolated when homoallylic alcohol **9** was subjected to the standard conditions without DMSO, verifying that **4a** should arise from compound **9** caused by Pd-hydride-mediated isomerization (Figure 1b). In the unoptimized Heck−Matsuda reaction of cyclic alkene **10** and **2d**, a clear suppression effect of the Pd-hydride-mediated alkene isomerization could also be observed (Figure 1c). Thus, we postulate that DMSO in the system might be able to accelerate the dissociation and reduce the lifetime of palladium hydride species **V**, presumably through coordination to the palladium center. This is in accordance with the fact that diaryl sulfoxide **7d** with low coordination ability had little effect on suppressing the formation of **4a**. The boost of the initial reaction rate could be explained by the accelerated dissociation of **V** and avoidance of undesired pathways, both leading to fast turnover of the palladium catalyst.

In summary, we have developed chiral-anion-mediated enantioselective Heck−Matsuda reactions with challenging acyclic alkenyl alcohols as the substrates, extending the application teritory of CAPT in transition metal catalysis.

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Various chiral ketones could be obtained with up to 97:3 er. Importantly, the presence of DMSO as additives is crucial for the reaction to suppress palladium-hydride-mediated side reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00152.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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