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Palladium-Catalyzed Asymmetric Trifluoromethylated Allylic Alkylation of Pyrazolones Enabled by α-(Trifluoromethyl)alkenyl Acetates

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Cite This: *Org. Lett.* 2021, 23, 5804–5808 Read Online

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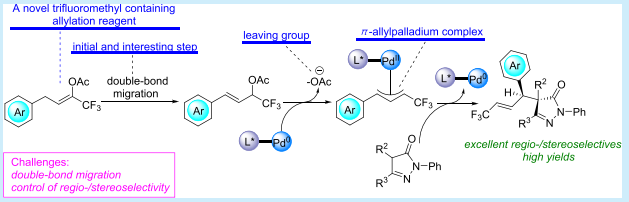
ABSTRACT: The first asymmetric trifluoromethylated allylic alkylation of pyrazolones using α-(trifluoromethyl)alkenyl acetates as a novel trifluoromethylated allylation reagent is described, affording various functionalized chiral pyrazolones containing a trifluoromethylated allyl substituent in high yields with excellent regio-/enantio-/diastereoselectivities. Mechanistically, the double-bond migration of α-(trifluoromethyl)alkenyl acetates in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene is initial and interesting step. More importantly, this study is of significance in providing a novel and widely applicable trifluoromethyl-containing allylation reagent.



The palladium-catalyzed asymmetric allylic alkylation (AAA) between a nucleophile and an allylic activated substrates is one of the most efficient methods to construct a chiral center in organic chemistry.[1] Various allyl precursors, such as allyl esters,[2] allyl alcohols,[3] and some other propylene derivatives,[4] have been used in the classic reaction. Recently, allyl carbonates have been met with great success with the cooperation of palladium catalysts and chiral ligands in AAA.[2] Despite these considerable advances, there is limited literature focused on developing new allylation reagents that can be widely used for AAA. In particular, to our knowledge, trifluoromethyl-containing allyl donors have rarely been reported, and they have been even more rarely applied to asymmetric reactions.[5] In sharp contrast, the introduction of fluorinated substituents into bioactive molecules has been generally accepted as a common strategy to improve physicochemical properties.[6] Hence the search for widely applicable allylation reagents with a fluorinated substituent is still highly desired.

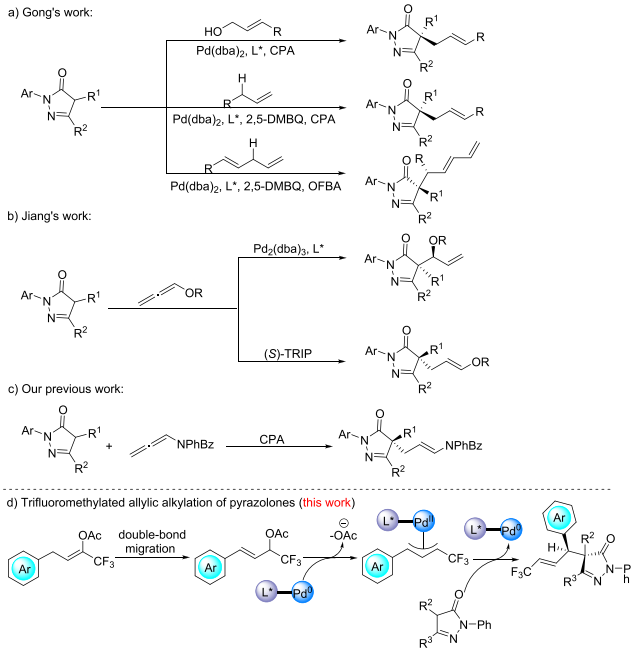
As part of our ongoing efforts in the synthesis of useful trifluoromethyl-containing molecules, α-(trifluoromethyl)-alkenyl trifluoromethanesulfonates have been discovered and widely applied in the synthesis of trifluoromethyl-containing compounds.[7] In particular, the discovery of the double-bond migration of α-(trifluoromethyl)alkenyl trifluoromethanesulfonates mediated by bases inspired our great interest in expanding this type of block into an asymmetric area. We envisioned that the double-bond migration of α-(trifluoromethyl)alkenyl esters enabled by a suitable base would furnish a generic trifluoromethylated allyl precursor.

With the outline in mind, we next selected pyrazolone as the nucleophile owing to our continuous study on the functionalization of this bioactive molecule.[8] Pyrazolones have drawn great attention due to their prevalent applications in the pharmaceutical industry.[9] To this end, the catalytic functionalization of pyrazolones, especially in the asymmetric realm, has received increasing research interest,[10] yet it remains challenging. It is worth noting that only a few of reports have disclosed the AAA of pyrazolones. The Gong group pioneered the study of the palladium-catalyzed AAA of pyrazolones using allylic alcohols[3a] or terminal olefins[11] as the allyl precursors (Scheme 1a). The Jiang group reported the selective asymmetric nucleophilic addition of pyrazolones with alkoxy allenes catalyzed by a chiral palladium complex or chiral Brønsted acid (Scheme 1b).[12] More recently, the Chen group reported the rhodium-catalyzed regio- and enantioselective allylic alkylation of pyrazolones with alkynes.[13] We have reported a chiral phosphoric acid (CPA)-catalyzed AAA of pyrazolones with allenamides as the allylation reagents (Scheme 1c).[8c] However, no asymmetric trifluoromethylated allylic alkylation of pyrazolones is available to date.

Herein we report the first asymmetric trifluoromethylated allylic alkylation of pyrazolones using α-(trifluoromethyl)

Received: June 12, 2021
Published: July 19, 2021

Scheme 1. Asymmetric Allylic Alkylation of Pyrazolones



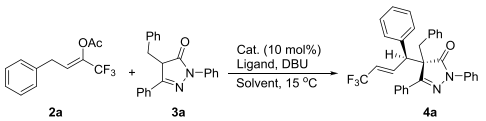
alkenyl acetates as novel allyl precursors (Scheme 1d). The combination of $Pd(OAc)_2$ and *R*-BINAP efficiently renders a high regio-/enantio-/diastereoselectivity in the trifluoromethylated allylic alkylation of pyrazolones with various α-(trifluoromethyl)alkenyl acetates.

We first investigated the leaving groups of α-(trifluoromethyl) alkenyl esters. After the optimization of several substrates (see the Supporting Information, Table S1), we proved that the transformation smoothly took place with excellent control of regio-/stereochemistry when acetoxy was used as the leaving group. The chiral ligands were next probed. (See the Supporting Information, Table S2.) The results showed that the reaction proceeded smoothly in the presence of L1, L2, or L3 (Table 1, entries 1−3) with the cooperation of $Pd(OAc)_2$ (10 mol %) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and *R*-BINAP exhibited the best selectivity (44% yield, >20:1 dr, 94% ee). Then, the palladium catalysts were explored (see the Supporting Information, Table S3, entries 1−5), and $Pd(OAc)_2$ was proved to be the best catalyst, with slightly higher enantioselectivity than $[Pd(ally)Cl]_2$ (Table 1, entries 1 and 4). Some other palladium catalysts, such as $PdCl_2$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$ had no catalytic activity for this reaction. The following screening of bases showed that the reaction did not occur when switching DBU to other organobases (see the Supporting Information, Table S3, entries 6−13), indicating that DBU was more efficient for the double-bond migration of α-(trifluoromethyl)alkenyl acetates. This speculation was proved in subsequent experiments.(See the Supporting Information, Table S4.) The examination of solvents (Table 1, entries 5−9) proved that tetrahydrofuran (THF) fitted the reaction best. Increasing the temperature resulted in a higher yield of **4a** but reduced enantioselectivity (Table 1, entry 10). Finally, after the careful optimization of the equivalents of ligand, DBU, and **2a** as well as the reaction time (see the Supporting Information, Table S5), the standard conditions of the palladium-catalyzed asymmetric trifluoromethylated allylic alkylation of pyrazolones were determined (Table 1, entry 11).

Various α-(trifluoromethyl)alkenyl acetates were subsequently prepared following our previous work on the synthesis of α-(trifluoromethyl)alkenyl triflates.[7a] As shown in Scheme 2, a wide range of branched α-(trifluoromethyl)alkenyl acetates can be readily furnished in high yields. In particular, the representative examples of alkyl- and heteroaryl-substituted substrates **2p** and **2o** were also obtained in good yields.

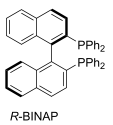
Further studies focused on the substrate scope (Scheme 3). The reaction of aryl-substituted α-(trifluoromethyl)alkenyl

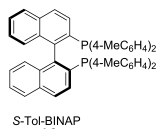
Table 1. Optimization of Reaction Conditions[a]

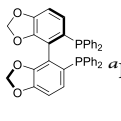


2a 3a 4a

entry	cat.	ligand	solvent	yield of **4a** (%)[b]	dr of **4a**[c]	ee of **4a** (%)[d]
1	$Pd(OAc)_2$	L1	1,4-dioxane	44	>20:1	94
2	$Pd(OAc)_2$	L2	1,4-dioxane	40	>20:1	−86
3	$Pd(OAc)_2$	L3	1,4-dioxane	30	>20:1	78
4[e]	$[Pd(allyl)Cl]_2$	L1	1,4-dioxane	52	>20:1	91
5	$Pd(OAc)_2$	L1	toluene	47	>20:1	92
6	$Pd(OAc)_2$	L1	CH_2Cl_2	55	>20:1	57
7	$Pd(OAc)_2$	L1	DME	45	>20:1	91
8	$Pd(OAc)_2$	L1	THF	40	>20:1	96
9	$Pd(OAc)_2$	L1	acetonitrile	58	>20:1	72
10[f]	$Pd(OAc)_2$	L1	THF	61	>20:1	90
11[g]	$Pd(OAc)_2$	L1	THF	80	>20:1	96


R-BINAP L1

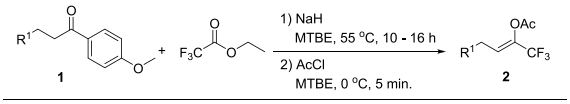

S-Tol-BINAP L2


L3

[a]Reactions were performed with **2a** (0.375 mmol), **3a** (0.25 mmol), cat. (10 mol %), ligand (22 mol %), and DBU (0.75 mmol) in 3.0 mL of solvent at 15 °C for 24 h. [b]Yield of isolated product. [c]Determined by ^1H NMR. [d]Determined by chiral high-performance liquid chromatography (HPLC). [e]5 mol % of $[Pd(allyl)Cl]_2$ was used. [f]Performed at 20 °C. [g]Standard conditions: **2a** (0.375 mmol), **3a** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), **L1** (12 mol %), and DBU (0.375 mmol) in 3.0 mL of THF at 15 °C for 52 h.

https://doi.org/10.1021/acs.orglett.1c01957
Org. Lett. 2021, 23, 5804−5808

Scheme 2. Preparation of α-(Trifluoromethyl)alkenyl Acetates[a]



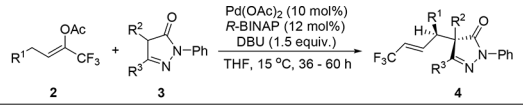
1

2

2a, R^1 = Ph, 86%
2b, R^1 = 2-MeC_6H_4, 83%
2c, R^1 = 3-MeC_6H_4, 84%
2d, R^1 = 4-MeC_6H_4, 86%
2e, R^1 = 4-$^iPrC_6H_4$, 90%
2f, R^1 = 2-$MeOC_6H_4$, 80%
2g, R^1 = 2-Naph, 85%
2h, R^1 = 4-PhC_6H_4, 86%
2i, R^1 = 4-FC_6H_4, 89%
2j, R^1 = 3-ClC_6H_4, 87%
2k, R^1 = 4-BrC_6H_4, 85%
2l, R^1 = 3-$CF_3C_6H_4$, 90%
2m, R^1 = 4-CNC_6H_4, 62%
2n, R^1 = 3,4,5-$(MeO)_3C_6H_4$, 91%
2o, R^1 = 2-thienyl, 88%
2p, R^1 = ^{n}hexyl, 84%

[a]See the Supporting Information for the detailed reaction conditions.

Scheme 3. Scope of Pd-Catalyzed Asymmetric Trifluoromethylated Allylic Alkylation[a]



2

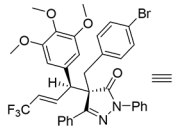
3

4

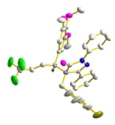
4a, R^1 = C_6H_5, 80%, > 20:1 dr, 94% ee
4b, R^1 = 2-MeC_6H_4, 90%, > 20:1 dr, 99% ee
4c, R^1 = 3-MeC_6H_4, 82%, > 20:1 dr, 94% ee
4d, R^1 = 4-MeC_6H_4, 81%, > 20:1 dr, 91% ee
4e, R^1 = 4-$^iPrC_6H_4$, 83%, > 20:1 dr, 99% ee
4f, R^1 = 2-$MeOC_6H_4$, 82%, > 20:1 dr, 97% ee
4g, R^1 = 2-Naph, 88%, > 20:1 dr, 94% ee
4h, R^1 = 4-PhC_6H_4, 85%, > 20:1 dr, 94% ee
4i, R^1 = 4-FC_6H_4, 84%, > 20:1 dr, 95% ee
4j, R^1 = 3-ClC_6H_4, 86%, > 20:1 dr, 92% ee
4k, R^1 = 4-BrC_6H_4, 79%, > 20:1 dr, 94% ee
4l, R^1 = 3-$CF_3C_6H_4$, 85%, > 20:1 dr, 96% ee
4m, R^1 = 4-CNC_6H_4, 70%, > 20:1 dr, 95% ee
4n, R^1 =3,4,5-$(MeO)_3C_6H_2$, 90%, > 20:1 dr, 94% ee
4o, R^1 = 2-thienyl, 81%, > 20:1 dr, 85% ee
4p, R^1 = ^{n}hexyl, 0%

4q, Ar = 3-MeC_6H_4, 88%, > 20:1 dr, 95% ee
4r, Ar = 1-Naph, 80%, > 20:1 dr, 96% ee
4s, Ar = 2-FC_6H_4, 72%, > 20:1 dr, 97% ee
4t, Ar = 3,5-$(CF_3)_2C_6H_3$, 87%, 10:1 dr, 95% ee
4u, Ar = 4-$NO_2C_6H_4$, 69%, > 20:1 dr, 77% ee

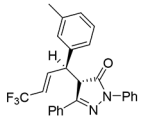
4v, R^3 = 2-MeC_6H_4, 89%, > 20:1 dr, 94% ee
4w, R^3 = 3-MeC_6H_4, 88%, > 20:1 dr, 92% ee
4x, R^3 = 4-MeC_6H_4, 83%, > 20:1 dr, 94% ee
4y, R^3 = 2-Naph, 81%, > 20:1 dr, 96% ee
4z, R^3 = 2-thienyl, 84%, 10:1 dr, 97% ee
4aa, R^3 = Me, 90%, 3:1 dr, 92% ee



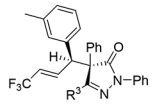
4ab, 89%, > 20:1 dr, 98% ee



X-ray structure of **4ab**



4ac, 0% yield



4ad, 0% yield

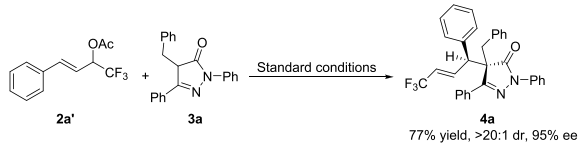
[a]Reactions were performed with **2** (0.75 mmol, 1.5 equiv), **3** (0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol %), *R*-BINAP (37.4 mg, 0.06 mmol, 12 mol %), and DBU (114 mg, 0.75 mmol, 1.5 equiv) in 3.0 mL of THF at 15 °C for 36−60 h.

acetates (**2a**−**2n**) with **3a** under the standard conditions showed that both electron-donating and electron-withdrawing substituents at the ortho, para, and meta positions were all well tolerated, and the corresponding products (**4a**−**4n**) were delivered in good yields with excellent regio-/enantio-/diastereoselectivities. In addition, 1,1,1-trifluoro-4-(thiophen-2-yl)but-2-en-2-yl acetate (**2o**) also reacted smoothly, and the desired product (**4o**) was formed in good yield with slightly lower enantioselectivity. However, the use of the alkyl-substituted substrate (**2p**) failed to provide the product (**4p**), which we attribute to the failure of double-bond migration in that molecule. (See the Supporting Information, Scheme S1, for the control experiment.)

A series of functionalized pyrazolones were next examined using **2c** as the allylic alkylation partner, and most of them furnished the corresponding products **4q**−**4ab** in high yields with excellent regio-/enantio-/diastereoselectivities. In the case of the nitro-substituted substrate, the corresponding product **4u** revealed a lower enantioselectivity, probably due to the coordination of the nitro group with the palladium catalyst. The 3-methyl variant (**4aa**) was obtained with markedly lower diastereoselectivity (3:1 dr) as a result of the lower steric hindrance, albeit it had high enantioselectivity (92% ee). Unfortunately, the reactions of four-unsubstituted pyrazolone and 4-phenyl pyrazolone did not occur under standard conditions (**4ac** and **4ad**). The relative and absolute configurations of the product **4ab** were determined by X-ray crystal analysis (CCDC 2070216).

A control experiment was subsequently performed to shed light on the reaction mechanism. As shown in Scheme 4, **4a**

Scheme 4. Control Experiment to Understand the Reaction Mechanism



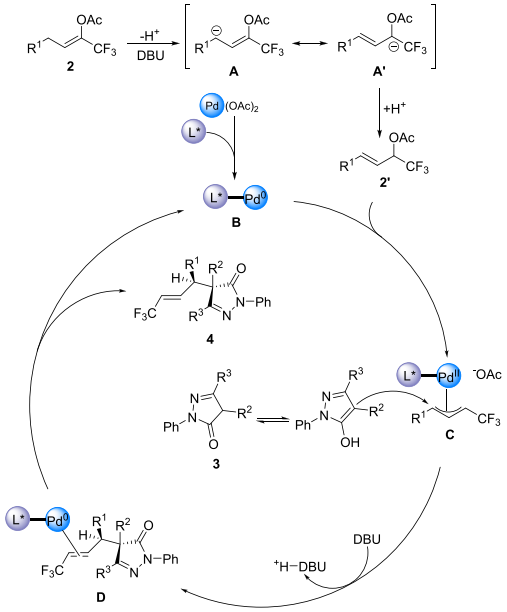
2a′

3a

4a
77% yield, >20:1 dr, 95% ee

was obtained in a maintained yield and with maintained stereoselectivity (77% yield, >20:1 dr, 95% ee) when the trifluoromethyl-containing allyl precursor **2a** was replaced with its double-bond shifted isomer **2a′**. A plausible mechanism was proposed for the asymmetric trifluoromethylated allylic alkylation according to the control reaction result and literature[14] (Scheme 5). Initially, the deprotonation of **2** in

Scheme 5. Proposed Reaction Mechanism



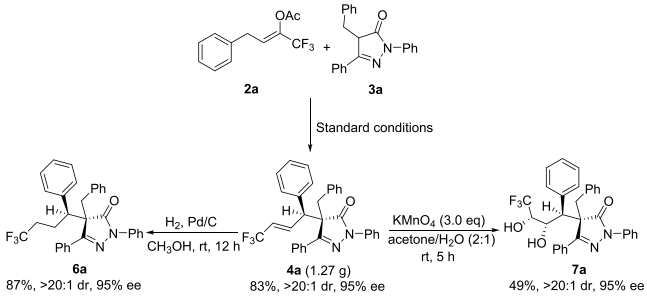
the presence of DBU generated **A** and its resonance form **A′** combined with a proton to furnish the precursor of trifluoromethylated allylic alkylation (**2′**). Then, the addition of **2′** with the resulting chiral Pd^0 complex (**B**) afforded the chiral π-allyl palladium complex **C**, which then underwent nucleophilic substitution with enolated pyrazolone to give the intermediate **D**. Finally, demetallization of **D** generated the

https://doi.org/10.1021/acs.orglett.1c01957
Org. Lett. 2021, 23, 5804−5808

desired product **4** accompanying the regeneration of the chiral Pd^0 complex (**B**) to the next catalytic cycle.

To demonstrate the utility of this process, gram-scale synthesis and transformations were carried out (Scheme 6).

Scheme 6. Gram-Scale Synthesis and Transformation of 4a



First, the reaction of **2a** and **3a** on a 3 mmol scale was performed to give the corresponding product **4a** in a maintained yield with maintained enantio-/diastereoselectivities (83% yield, >20:1 dr, 95% ee) in comparison with the small scale. The catalytic hydrogenation of **4a** with hydrogen on Pd/C was able to give **6a** in good yield with maintained stereoselectivity. Furthermore,**4a** can be oxidized with potassium permanganate, and the corresponding product (*cis*-diol, **7a**) was obtained in 49% yield with >20:1 dr and 95% ee. The configuration of the hydroxyl groups in **7a** was determined by ^{1}H NMR, hydrogen−deuterium exchange ^{1}H NMR, and COSY NMR. (See the Supporting Information for copies of the **7a** NMR spectrum.) As such, the chiral pyrazolones bearing a trifluoromethylated allylic substituent could be diversified by the available classical methods.

In summary, we have developed the first and efficient palladium-catalyzed asymmetric trifluoromethylated allylic alkylation of pyrazolones using α-(trifluoromethyl)alkenyl acetates as novel trifluoromethyl-containing allyl precursors. This strategy shows a broad substrate scope in terms of both the α-trifluoromethyl alkenyl acetates and the pyrazolones to afford an array of functionalized chiral pyrazolones containing a trifluoromethylated allyl substituent in high yields with excellent enantio-/diastereoselectivities. This work not only is valuable in the construction of various chiral trifluoromethylated allylic pyrazolones but also provides a novel and widely applicable trifluoromethyl allylation reagent. Further application of this trifluoromethyl allylation reagent is currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01957.

Experimental details, characterization data, and copies of spectra (PDF)

Accession Codes

CCDC 2070216 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the National Natural Science Foundation of China (no. 21878037). We also acknowledge Prof. Yi Luo, Dr. Yuming Song, and Dr. Ying Peng (Dalian University of Technology, China) for valuable discussions.

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https://doi.org/10.1021/acs.orglett.1c01957
Org. Lett. 2021, 23, 5804−5808