

Synthesis of Trifluoromethylated Tetrasubstituted Allenes via Palladium-Catalyzed Carbene Transfer Reaction

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excellent yield. This reaction proceeds via oxidative addition of a

 Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02638
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 ABSTRACT: Herein, we report on the palladium-catalyzed synthesis of trifluoromethylated, tetrasubstituted allenes from vinyl bromides and trifluoromethylated diazoalkanes in good to
 Palladium catalyst THF, 60 °C, 12 h
 Ar3 (CF3)
 Key features - high yields - simple catalyst - simple precursors - gram-scale synthesis

Pd(0) complex with vinyl bromide. Subsequent base-promoted reductive elimination generates the allene. This methodology provides an efficient strategy even on gram scale to valuable trifluoromethylated, tetrasubstituted allenes under mild reaction conditions. The allene products can be used in acid catalyzed cyclization reactions to give trifluoromethylated indene products.

llenes are an intriguing class of polyunsaturated hydro-**A**carbons and feature distinct properties that render allenes an important strategic building block for a diverse array of organic synthesis applications.^{1,2} Among these, the activation with Lewis acids is among the most important reactions to quickly increase molecular complexity.³ A particularly intriguing group of allenes are fluorinated or trifluoromethylsubstituted allenes that are valuable hydrocarbons for further derivatization.4-7 Owing to the importance of fluorine in pharmaceutical, agrochemical, and materials chemistry,⁸ the synthesis of fluorinated allenes is thus of high interest, as they can be readily functionalized for further applications. Currently available strategies for the synthesis of fluorinated allenes comprise the utilization of fluorinated, unsaturated building blocks that can be transformed to allenic products^{5,6} or the introduction of either fluoride or a trifluoromethyl group onto an appropriately functionalized, unsaturated reagent to access mono-, di-, and trisubstituted fluorinated allenes.' Despite this progress, the catalytic synthesis of tetrasubstituted trifluoromethylated allenes still remains a synthetic challenge. One of the rare examples for the synthesis of such allene derivatives involves the use of propargylic alcohols that undergo dehydration in the presence of Lewis acids, yet with strict limitations in yield and the utilization of highly specialized fluorinated, propargylic alcohols (Scheme 1a).⁶ The synthesis of tetrasubstituted allenes even today represents an important task in organic synthesis methodology.^{8,9} In this context, the Lin group recently reported on the palladium-catalyzed coupling of aryldiazoacetates with vinyl bromides to access ester-substituted, tetrasubstituted allene products 11 (Scheme 1c, top).9

Based on our interest in fluorine chemistry,¹⁰ we became intrigued in the synthesis of trifluoromethylated, tetrasubstituted allenes using trifluoromethylated donor/acceptor diazoalkanes (Scheme 1c, bottom).¹¹ The latter have emerged in recent years as important reagents in the synthesis of trifluoromethylated cyclopropa(e)nes,^{10b,12} gem-difluoro olefins,^{10a,13} trifluoromethylated heterocycles,^{10c,14} and other important trifluoromethylated building blocks¹⁵ (Scheme 1b) and possess distinct properties to conventional estersubstituted donor/acceptor diazoalkanes.

We hypothesized that vinyl bromides are suitable precursors to access tetrasubstituted allenes via a metal-catalyzed crosscoupling reaction with fluorinated donor/acceptor diazoalkanes that could then serve as a platform for further derivatization, e.g. by intramolecular acid catalyzed cyclization, to access trifluoromethylated indene derivatives. We therefore initiated our investigations by studying the reaction of vinyl bromide **9a** with the trifluoromethylated donor/acceptor diazoalkane **4a** using palladium-based catalysts. The latter should allow oxidative insertion into the $C(sp^2)$ –Br bond of vinyl bromide, which should be a suitable intermediate for a subsequent cross-coupling reaction step.

Moreover, we assumed that basic additives are a pivotal component to promote the reductive elimination step and to capture HBr that is released in the coupling reaction. Indeed, the base had a significant influence on the reaction yield (Table 1, entries 1–7). Of all bases studied, only K_2CO_3 proved compatible and the desired allene product 12a was obtained in 72% yield when using dpph as the ligand and Pd(OAc)₂ as the palladium source (Table 1, entry 7). Further studies then focused on the reaction yield was observed with different variants of the dpph ligand (Table 1, entries 8–10). Surprisingly, BINAP proved incompatible and only a very low yield was observed (Table 1, entry 11, 5%). To further

Received: August 6, 2020



Scheme 1. Synthesis of Fluorinated Allenes and Applications of Trifluoromethyl-Substituted Donor/ Acceptor Diazoalkanes

a) recent progress on the synthesis of fluorinated tetrasubstituted allene



b) Applications of trifluoromethylated donor/acceptor diazoalkane



improve the reaction yield, we next studied different monodentate phosphine ligands. Buchwald-type ligands proved inferior in this transformation, and low yields of the allene product were observed, at best (Table 1, entry 12–15). Similarly, tri-o-tolyl phosphine gave only a poor yield (Table 1, entry 16). Very unexpectedly, the most simple and readily available triphenyl phosphine gave by far the best yields and allene **12a** was obtained in excellent yield (Table 1, entry 19, 95%).¹⁶ When the reaction was studiend in the absence of a ligand, only trace amounts of the allene were observed (Table 1, entry 20). Similarly, the use of $Pd_2(dba)_3$ resulted in a significantly reduced yield (Table 1, entry 21), which might be reasoned by inefficient catalyst formation.

After establishing reaction conditions to access trifluoromethylated, tetrasubstituted allenes in high yields, we next embarked on the substrate scope and first studied the influence of the 2,2-diaryl vinyl bromide (9) reaction partner (Scheme 2). Different symmetrically substituted vinyl bromides reacted in excellent yield to the trifluoromethyl-substituted allene product, and both halogen and electron-donating groups were well tolerated under the present conditions. Similarly, different unsymmetrically substituted vinyl bromides reacted smoothly and the tetrasubstituted allene was obtained in all cases in excellent yield, disregarding the substitution pattern of one of the aromatic rings of the vinyl bromide reaction partner. Even ortho substituents were well tolerated under the present conditions, and the allene products were obtained in very good yield. Only in the case of a bromo-substituent, the yield of the allene product 12i was slightly reduced, which might be

Table 1. Optimization of Reaction Conditions

	Br N2	Pd(OAc) ₂ (10 mol%) ligand (15 mol%) base (1.5 equiv)	Ph CF ₃
Ph	Ph Ph CF ₃	THF, 60 °C, 12 h	
9a	4a		Ph Ph 12a
no. ^a	ligand ^b	base	yield ^c (%)
1	dpph	CsOAc	15
2	dpph	КОН	9
3	dpph	K_2CO_3	72
4	dpph	Li ₂ CO ₃	8
5	dpph	LiOH	3
6	dpph	NaOAc	5
7	dpph	NEt ₃	8
8	dppb	K_2CO_3	74
9	dppe	K_2CO_3	76
10	dppf	K_2CO_3	71
11	rac-BINAP	K ₂ CO ₃	5
12	DavePhos	K ₂ CO ₃	4
13	SPhos	K_2CO_3	traces
14	XPhos	K_2CO_3	traces
15	RuPhos	K_2CO_3	traces
16	PoTol ₃	K ₂ CO ₃	6
17	PAd ₂ nBu	K ₂ CO ₃	72
18	PFur ₃	K_2CO_3	67
19	PPh_3	K_2CO_3	95
20	-	K_2CO_3	traces
21 ^d	PPh ₃	K ₂ CO ₃	8

^aReaction condtions: **9a** (0.2 mmol), **4a** (0.3 mmol, 1.5 equiv), catalyst (10 mol %), ligand (15 mol %), and base (0.3 mmol, 1.5 equiv) were dissolved in the solvent indicated (2.5 mL) and stirred at 60 °C for 12 h. ^bdppf, 1,1'-bis(diphenylphoshino)ferrocene; dpph, 1,6-bis(diphenylphoshino)hexane; dppb, 1,6-bis(diphenylphoshino) butane; dppe, 1,6-bis(diphenylphoshino)ethane; XPhos, 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl; RuPhos 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl; CPields by ¹⁹F NMR spectroscopy of the crude reaction mixture using PhCF₃ as internal standard. ^dWith 5 mol % Pd₂(dba)₃ as catalyst precursor.

reasoned by competitive oxidative insertion of the palladium catalyst into the Aryl–Br bond. Importantly, carbocyclic or sulfur-containing heterocycles proved compatible to the present reaction conditions and the corresponding tetrasubstituted allene products were obtained in very high yield. We further studied the application of exocyclic vinyl bromides using dibenzosubera(e)ne derived vinyl bromides. In both cases, the coupling reaction with trifluoromethylated donor/ acceptor diazoalkane proceeded to give **12s**,**t** in high yields (Scheme 3). In this context, we also studied the application of different substitution patterns of the trifluoromethyl-substituted diazoalkane and could obtain the coupling product in excellent yield.

Next, we studied the limitations and applicability on gram scale of the present methodology (Scheme 4). To test the applicability of vinyl chlorides, we studied the coupling reaction of 2,2-diphenyl vinyl chloride (13); however, the reaction yield dropped significantly and only 32% of the allene product 12a was obtained. When *trans-* β -bromo-styrene 14 was studied, the allene product was not formed and only the decomposition of the diazoalkane 4a was observed, which might be reasoned by a hampered migration step of the fluorinated carbene that results in a preferred decomposition





Scheme 3. Further Evaluation of Substrate Scope



reaction of the palladium carbene intermediate. The reaction of alkyl-aryl vinyl bromide **15** led to formation of a complex, inseparable mixture. The major products could not be isolated, yet NMR data indicate the formation of an allene and a diene product, the latter resulting from β -H elimination. Finally, when performing the reaction on gram scale, the desired tetrasubstituted allene could be obtained with almost identical yield as above (cf. Scheme 2, 12b).

Scheme 4. Limitations and Application on Gram Scale



Last, we studied the application of the tetrasubstituted allene product in acid-catalyzed cyclization reactions. In the presence of triflic acid, allene **12b** smoothly underwent chemoselective cyclization to give the trifluoromethylated indene product **16** in excellent yield. When employing 5 mol % of Yb(OTf)₃ as a Lewis acid catalyst, the allene could be activated toward intramolecular Friedel–Crafts reaction to give the indene product **16** and **17** in high yield (Scheme 5).





From a mechanism perspective, we assume that the present reaction proceeds via a Pd(0) catalyst that undergoes an initial oxidative insertion reaction with vinyl bromide 9a to give an intermediate Pd(II) complex 19. This complex can now react with the trifluoromethylated donor/acceptor diazoalkane 4a followed by 1,2-migration to give the Pd-allyl complex 21/21' that finally undergoes base-assisted reductive elimination to regenerate the catalyst and the tetrasubstituted allene product 10a (Scheme 6). A potential β -fluoride elimination would lead to the formation gem-difluoro olefins, yet this step would result in formation of an unfavorable high oxidation state Pd(II)BrF complex, for which it is difficult to regenerate the Pd catalyst.

In summary, we herein report on the palladium-catalyzed synthesis of trifluoromethylated, tetrasubstituted allenes. A simple and readily available palladium catalyst and phosphine ligand provide an easy-to-handle procedure to challenging tetrasubstituted allenes in excellent yield (24 examples, up to 96% yield). Gram-scale experiments and application of trifluoromethylated tetrasubstituted allenes further present the practicality of this method. A possible mechanism was

Scheme 6. Putative Reaction Mechanism



proposed involving oxidative addition of a Pd(0) complex with vinyl bromide and a β -H elimination process to regenerate the active palladium catalyst and the final tetrasubstituted allenes product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02638.

Experimental procedures, characterizations, analytical data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

R.M.K. thanks the German Science Foundation for financial support. C.P. thanks the China Scholarship Council for the support with a PhD scholarship.

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(16) For further details on the reaction optimization, see the Supporting Information.