Organic LETTERS

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

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Highly Diastereoselective Synthesis of Trifluoromethyl Indolines by Interceptive Benzylic Decarboxylative Cycloaddition of Nonvinyl, Trifluoromethyl Benzoxazinanones with Sulfur Ylides under Palladium Catalysis

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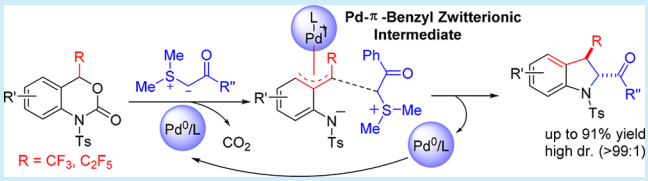
Supporting Information

ABSTRACT: A highly diastereoselective synthesis of trifluoromethyl-substituted indolines under palladium catalysis is disclosed. The reaction proceeds by interceptive decarboxylative benzylic cycloaddition (IDBC) of nonvinyl, trifluoromethyl benzoxazinanones with sulfur ylides. The palladium−π-benzyl zwitterionic intermediates are suggested for this transformation, and this would be the first example of an IDBC reaction.



Heterocyclic compounds containing a fluorine (F) or trifluoromethyl (CF_3) group on their core moieties are well studied in the field of pharmaceuticals and agrochemicals, and some of them are successfully distributed in the drug market.[1] Among them, fluorinated indoles and oxindoles have received a great deal of attention in the literature because of the exceptional influence of the fluorine atom in terms of chemical and physiological stability.[2] On the other hand, the CF_3-substituted indolines are not developed, despite the attractive biological properties of indolines, which are well distributed in natural products and pharmaceuticals.[3] We report herein the highly diastereoselective synthesis of medicinally attractive CF_3-substituted indolines by interceptive decarboxylative benzylic cycloaddition (IDBC) via a palladium−π-benzyl zwitterionic intermediate.

The interceptive decarboxylative allylic cycloaddition (IDAC) reaction of cyclic allylic carbamates under palladium catalysis[4] is a sophisticated extension of the Tsuji−Trost decarboxylative allylation (DA) reaction.[5] A zwitterionic π-allyl palladium complex is a reactive intermediate that is then intercepted by a sufficiently reactive substrate, providing a medium-sized ring skeleton.[4] Among the cyclic allylic carbamates in this transformation, vinyl benzoxazinanones **1** are efficient multifarious synthons for the IDAC reaction to afford biologically pertinent heterocyclic molecules.[6] The palladium−π-allyl zwitterionic intermediate **I** generated from **1** was disclosed by Tunge et al. and successfully trapped with benzylidene malononitriles, producing tetrahydroquinolines via the [4 + 2] IDAC reaction.[6a,b] This seminal work stimulated chemists into further extensions of the IDAC reaction of **1** with other interceptors such as sulfur ylides **3**,[6c−e] activated alkenes,[6a,b,f] enals,[6g,h] ketenes,[6i] and isatins[6j] under palladium or other metal catalysis (Figure 1a).

Although the IDAC reactions of **1** have significant potential with many reactive interceptive substrates, a diversity of benzoxazinanone **1** are highly limited to "vinyl"-substituted compounds because of the vital role of the vinyl group in generating a palladium-stabilized π-allyl complex. Xiao expanded the [4 + 1] interceptive decarboxylative cycloaddition reaction to

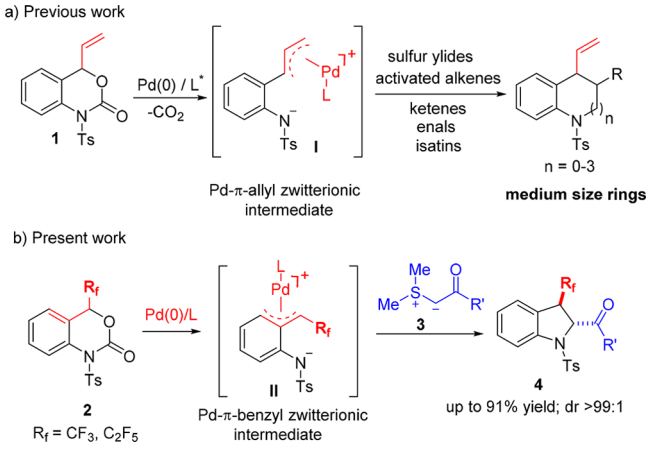


Figure 1. (a) IDAC reaction via zwitterionic π-allyl palladium complex (previous work); (b) IDBC reaction via zwitterionic π-benzyl palladium complex (this work).

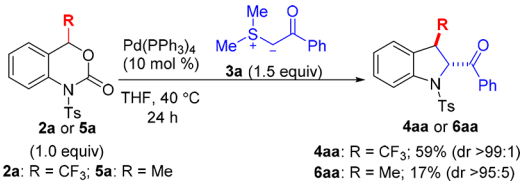
Received: January 23, 2018

DOI: 10.1021/acs.orglett.8b00237
Org. Lett. XXXX, XXX, XXX−XXX

the propargylic analogues of **1** with sulfur ylides **3** under copper catalysts, furnishing a series of alkynyl indolines.[6e] However, the fundamental issue of the use of a nonvinyl substrate remains a great challenge.[6] In this context, we envisaged the generation of palladium−π-benzyl zwitterionic intermediate **II**, an isoelectronic variant of Tsuji−Trost allylic substitution, could be equally possible, but in fact, there is no example of this type of benzylic cycloaddition. The reaction involving π-benzyl−palladium complex is rather limited to the acyclic reactions.[7] The low reactivity of benzylic substitution of this type is explained by the aromaticity of the benzene ring, while allylic compounds are inherently reactive. Recently, a Suzuki−Miyaura cross-coupling reaction with secondary α-(trifluoromethyl)benzyl tosylates was reported by Tredwell et al.[7k] Inspired by this result, we assumed that the CF_3 group at the benzylic position (C4) induces a strong negative inductive effect on the neighboring carbon, allowing the benzylic carbon to become electron deficient. Thus, a highly electrophilic palladium−π-benzyl zwitterionic intermediate **II** should be generated by oxidative addition of Pd(0) to amenable IDBC reaction to produce biologically important CF_3-indolines (Figure 1b). These results are the first example of a palladium-catalyzed IDBC reaction using nonvinyl benzoxazinanones **2**. The CF_3 group plays an important role in this transformation.

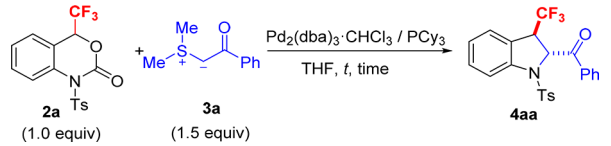
First, we designed the previously unknown CF_3-benzoxazinanone **2a** and investigated its suitability for IDBC reactions.[4,5] We rapidly discovered that CF_3-benzoxazinanone **2a** reacted with sulfur ylide[8] **3a** under palladium catalysis to provide the desired [4 + 1] IDBC product **4aa** in moderate yield. This reaction performed with $Pd(PPh_3)_4$ (10 mol %) at 40 °C in THF gave CF_3-indoline **4aa** in 59% yield with high diastereoselectivity (dr >99:1). CF_3 effect is very impressive as the methyl-substituted benzoxazinanone **5a** gave Me-indoline **6aa** only in 17% yield (dr >95:5) (Scheme 1). Encouraged by this result, we optimized the

Scheme 1. Initial Attempts for IDBC Reaction of 2a or 5a with 3a Using $Pd(PPh_3)_4$ Catalyst



reaction of **2a** with **3a** by screening different phosphine ligands (dppe, dppf, PEt_3, *t*BuXPhos, PCy_3, and Binap) and solvents in the presence of Pd(0) catalyst (Table 1 and Tables S1 and S2 in Supporting Information). Gratifyingly, **4aa** was obtained in excellent yield (98%) and very high diastereocontrol (dr = 99:1) using PCy_3 (10 mol %) and $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) at 40 °C in THF for 1 h (run 1, Table 1). The amount of Pd catalyst could be reduced to 1 mol % and 2.5 mol %, resulting in the required product with moderate yields (Table S2). No reaction occurred in the absence of the palladium catalyst (runs 3 and 4), and the absence of PCy_3 gave **4aa** in low yield after longer reaction time (run 2). Increasing the reaction temperature from rt to 40 °C accelerated the reaction significantly from 24 to 1 h (runs 1 and 5). The Me-substituted benzoxazinanone **5a** underwent IDBC and gave Me-indoline **5aa** in 42% yield under the same reaction conditions optimized for **2a**, albeit only after extended reaction time (run 6: 42%, 24 h vs run 1: 98%, 1 h).

Table 1. Effects of Pd, Ligand, and Temperature[a]

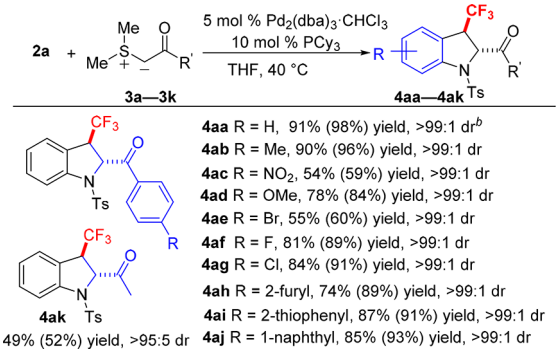


run	Pd	PCy_3	t (°C)	time (h)	yield[b] (%)	dr[c]
1	yes	yes	40	1	98	>99:1
2	yes	no	40	24	24	>99:1
3	no	yes	40	24	NR	
4	no	no	60	24	NR	
5	yes	yes	rt	24	91	>99:1
6[d]	yes	yes	40	24	42[e]	>95:5

[a]Experiments were performed with **2a** (0.15 mmol), **3a** (0.225 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0075 mmol or absence), PCy_3 (0.015 mmol or absence) in 1.0 mL of dry THF. [b]Yields are ^{19}F NMR yields with internal standard $PhCF_3$. [c]Diastereomeric ratio was determined by ^{19}F NMR analysis of the reaction mixture. [d]Compound **5a** was used instead of **2a**. [e]Yield of **6aa**.

With the optimized reaction conditions in hand, the generality of the IDBC reaction was examined by reacting CF_3-benzoxazinanone **2a** with sulfur ylides **3a−k**. The results are summarized in Scheme 2. Sulfur ylides **3b,d**, which have electron-

Scheme 2. Scope of Sulfur Ylides 3[a]



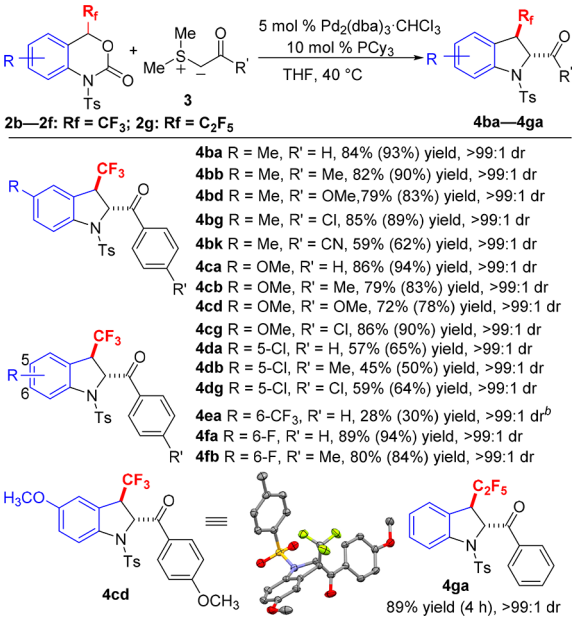
[a]Experiments were performed with **2a** (0.15 mmol), **3a−k** (0.225 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0075 mmol), PCy_3 (0.015 mmol) in 1.0 mL of dry THF with stirring at 40 °C for 1−8 h. Yields and ^{19}F NMR yields with internal standard $PhCF_3$ are shown in parentheses. The dr was determined by ^{19}F NMR analysis of the reaction mixture. [b]Reaction performed with 1 mmol scale of **2a** and 1.5 mmol of **3a** (see the Supporting Information for details).

donating groups (Me and OMe), afforded the desired CF_3-indolines in excellent yields (90% of **4ab** and 78% of **4ad**), whereas the sulfur ylide **3c** with an electron-withdrawing group (NO_2) resulted in moderate yield (54% of **4ac**). Halogen-substituted sulfur ylides **3e−g** also underwent IDBC with moderate to very good yields (55% of **4ae**, 81% of **4af**, and 84% of **4ag**). The heteroaryl systems **3h,i** (2-furyl and 2-thiophenyl), extended π-conjugate naphthalene-derived sulfur ylide **3j**, and aliphatic acyl-stabilized ylide **3k** are also well tolerated to afford the CF_3-indolines **4ah** (74%), **4ai** (87%), **4aj** (85%), and **4ak** (49%). All of these reactions proceeded with complete control over diastereoselectivity (Scheme 2).

Next, a range of differently substituted CF_3-benzoxazinanones **2b−f** was examined to delineate the generality of the IDBC reaction (Scheme 3). Various substituents on the benzene ring with electronically dissimilar groups at different positions were

DOI: 10.1021/acs.orglett.8b00237
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of Benzoxazinanones 2[a]

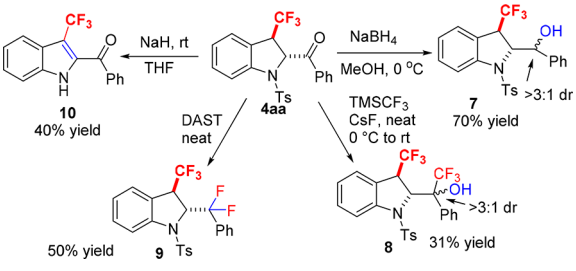


[a]Unless otherwise noted, the reaction was performed with 0.15 mmol scale of **2** as mentioned in Scheme 2. The dr values and yields were calculated as mentioned in Scheme 2. [b]10 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 20 mol % of PCy_3 were used.

well tolerated in moderate to good yields with high diastereoselectivities. The halogen-substituted CF_3-benzoxazinanones **2d** and **2f** (Cl and F) produced CF_3-indolines **4** in moderate to good yields (57% of **4da** and 89% of **4fa**). Substrates **2b**,**c** with electron-donating groups on the benzene ring such as Me and OMe were successfully transformed into corresponding CF_3-indolines in excellent yields (84% of **4ba** and 86% of **4ca**) with high dr. An electron-withdrawing CF_3 group on the benzene ring of **2e** reduced the yield of CF_3-indoline **4ea** by 28%. The *trans*-configuration of **4** was confirmed by the X-ray crystallographic analysis of **4 cd** (CCDC 1556229). The pentafluoroethyl (C_2F_5)-benzoxazinanone **2g** also underwent the IDBC reaction smoothly to furnish C_2F_5-indoline **4ga** with excellent yield of 89% and high selectivity (>99:1) in 4 h (Scheme 3).

To demonstrate the synthetic utility of CF_3-indolines **4**, several reactions were carried out, as shown in Scheme 4. CF_3-

Scheme 4. Derivatization of CF_3-Indoline 4aa



indoline **4aa** was successfully transformed to alcohols **7** and **8** having three consecutive stereogenic centers by reduction with $NaBH_4$ (70% yield) and by reaction with Me_3SiCF_3 (31% yield), respectively (diastereoselectivities are >3:1). Indoline **4aa** was also converted to difluorinated derivative **9** with 50% yield by the reaction with DAST. Furthermore, **4aa** was converted into CF_3-substituted indole **10** with 40% yield in the presence of NaH in THF (Scheme 4).

A plausible catalytic cycle of the Pd-catalyzed IDBC reaction of **2a** with **3a** to **4aa** is depicted in Figure 2, based on the reported

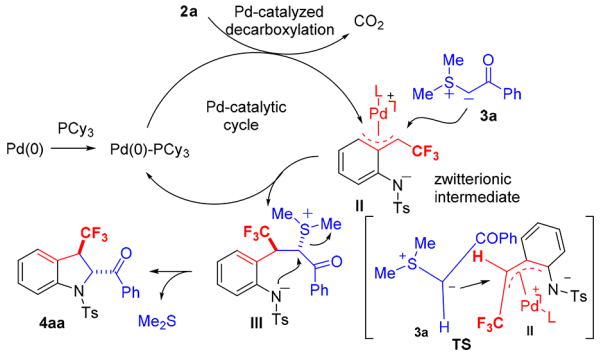


Figure 2. Proposed mechanism including stepwise formation of zwitterionic intermediate **II**.

mechanism of the IDBC reaction of **2** with **3a** via the Pd–π-benzyl zwitterionic intermediate.[6a−c] The catalytic cycle is first initiated by the oxidative addition of Pd(0) with **2a** followed by decarboxylation, which leads to the benzyl–Pd(II) zwitterionic intermediate **II**. Intermediate **II** is very electrophilic due to the CF_3 group, and subsequently, a new C–C bond is formed by the addition of sulfur ylide **3a** to complex **II**, diastereoselectively resulting in the zwitterionic complex **III** with the reductive elimination of the Pd(0) catalyst. Finally, the zwitterionic complex **III** undergoes an intramolecular S_N2-type *anti*-periplanar reaction from nitrogen to the stereogenic carbon center attached to the sulfonium moiety in **III**, furnishing the corresponding *trans*-CF_3-substituted indoline **4aa** with the release of Me_2S. The highly diastereoselective formation of the *trans*-isomer of **4aa** could be explained as follows. The zwitterionic complex **III** can be formed via transition state **TS**, due to the favorable steric repulsion between CF_3 and SMe_2 moieties (Figure 2).

In conclusion, we disclose a novel method to synthesize diverse substituted trifluoromethyl indolines **4** from **2** under palladium catalysis in a highly diastereoselective fashion. In this transformation, a CF_3 substitution at the benzylic position of benzoxazinanones **2** is highly effective. Pentafluoroethyl (C_2F_5) substitution was also suitable under the same reaction conditions, whereas a nonfluorinated Me group gave a lower yield. The electron-withdrawing nature of the perfluoroalkyl group played a crucial role in this transformation. A series of CF_3-benzoxazinanones **2** was smoothly reacted with sulfur ylides **3** under palladium catalysis in the presence of tricyclohexylphosphine (PCy_3) to provide pharmaceutically attractive CF_3-subsituted indolines **4** in high to excellent yields up to 91% with high diastereoselectivities greater than 99:1 dr. This type of IDAC reaction is belived to use vinyl-substituted substrates, thus, these results are the first example of a palladium-catalyzed nonvinyl, IDBC reaction, and CF_3 is highly advantageous for the efficient transformation. Moreover, the CF_3-indolines **4** are prospective synthetic building blocks for biologically attractive drug candidates.[1] Extension of this work is currently in progress, including isolation of Pd–π-benzyl zwitterionic intermediates and enantioselective variants of the reaction (for preliminary studies of the asymmetric reaction, see Table S3).

DOI: 10.1021/acs.orglett.8b00237
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00237.

Syntheses and NMR spectra (PDF)

Accession Codes

CCDC 1556229 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

This work was supported by JSPS KAKENHI Grant No. JP 16H01142 in Middle Molecular Strategy, and ACT-C from the JST Agency (JPMJCR12Z7).

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DOI: 10.1021/acs.orglett.8b00237
Org. Lett. XXXX, XXX, XXX−XXX