Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Copper-Catalyzed Radical Difluoroalkylation and Redox Annulation of Nitroalkynes for the Construction of C2-Tetrasubstituted Indolin-3-ones

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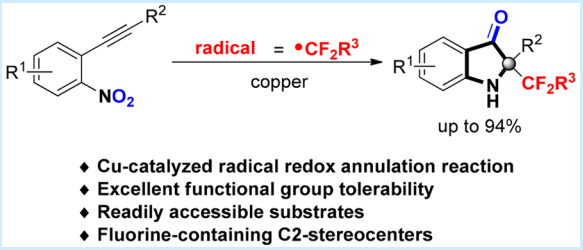
Supporting Information

ABSTRACT: An efficient and convenient method with wide applicability for the synthesis of C2-tetrasubstituted indolin-3-ones via copper-catalyzed redox cycloisomerization of nonprefunctionalized nitroalkynes has been developed. This protocol features simple operation, readily available starting materials, good functional group tolerance, broad scope, and diboron as the reductant.



Indolin-3-ones are one of the privileged core skeletons that continually appear in natural products and pharmacologically active compounds.[1] Among them, pseudoindoxyls bearing C2 stereocenters have emerged as crucial intermediates that are generally included in diverse biologically compounds and pharmaceutical agents such as halichrome A,[2] duocarmycins C_1 and B_1,[3] cephalinone,[4] LipidGreen and austamide,[5] etc. (Figure 1). The intramolecular cyclization of an *o*-nitroalkyne is one of

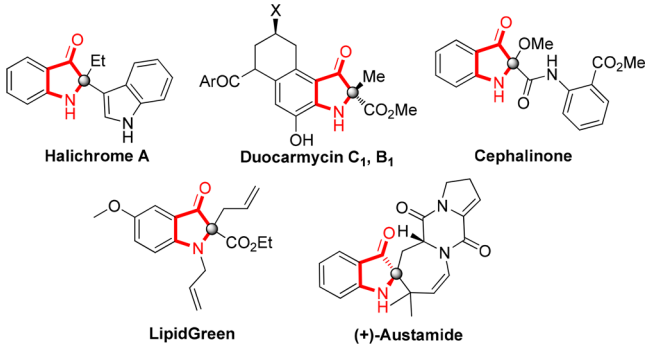
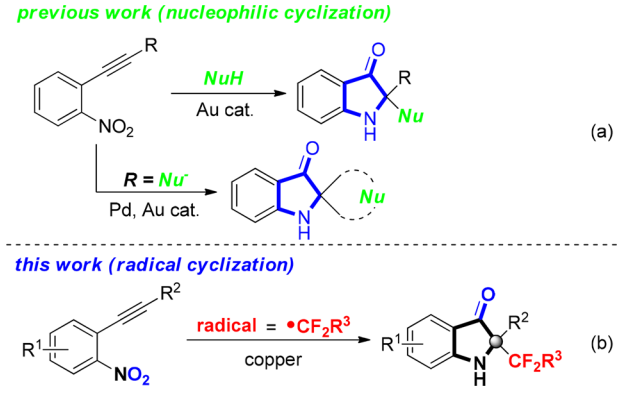


Figure 1. Several bioactive molecules containing C2-tetrasubstituted indolin-3-ones.

the most simple and convenient routes for the synthesis of C2-tetrasubstituted 3-oxindole derivatives. In 2015, Harrity's group reported a Cu-promoted cyclization of 2-nitrophenyl iodoacetylenes for the synthesis of 2-iodoisatogens,[6] although it is of note that C2 is not a stereocenter in this case. Formation of non-carbon quarternary center pseudoindoxyls through transition-metal-catalyzed inter- or intramolecular nucleophilic group attack on C2 was reported (Scheme 1a).[2,7] Among the metal-catalyzed activations of nitroalkynes for the construction

Scheme 1. Recent Advances in the Synthesis of Indolin-3-ones Bearing a C2-Tetrasubstituted Center



of internal cycloisomerization, noble metals such as palladium and gold catalysts were widely used species in the representative strategies.[2,6−8] The incorporation of difluoroalkyl groups into organic compounds has emerged as a substantially attractive tactic, since it can improve the biological and physicochemical properties of the parent molecules.[9,10] Because of the significance and effectiveness of indolin-3-one compounds, finding a straightforward and efficient way of incorporation of difluoroalkyl groups into the indolin-3-one skeleton from readily accessible substrates is highly desirable.

We recently reported that bromodifluoroacetate could serve as a source of difluoroalkyl radical under Cu/B_2pin_2 catalysis, and most remarkably, this difluoroalkyl radical exhibits unique

Received: November 27, 2017

DOI: 10.1021/acs.orglett.7b03678
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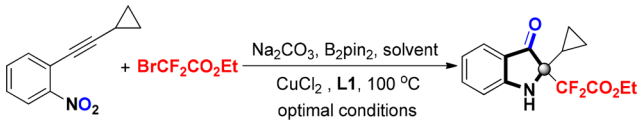
reactivity.[9] Although significant advances have been achieved in fluoroalkylation using functionalized fluoroalkyl reagents, direct and efficient strategies for the synthesis of tetrasubstituted carbons containing difluorinated functional groups has not been reported to date to our knowledge. As part of our ongoing interest in the reactivity of difluoroalkylated carbon radicals catalyzed by the copper/B_2pin_2 system, herein we report a facile Cu-catalyzed radical difluoroalkylation/redox annulation of 2-alkynylnitroarenes to produce fluorine-containing C2-tetrasubstituted indolin-3-one derivatives in moderate to excellent yields (Scheme 1b). There are several obvious advantages of our strategy over the precedent reports: (1) one-pot protocol instead of stepwise operation; (2) cheaper and low-toxicity copper catalyst in place of noble-metal catalysts; (3) unique catalytic system with diboron as the reductant; (4) novel radical mechanism instead of the precedent nucleophilic mechanism; (5) formation of a fluorine-containing non-carbon quaternary center. However, the major challenges of this strategy are twofold: (1) the nitro group could be reduced to an amino group in the presence of diboron as the reductant before cyclization,[11] and (2) the difluoroalkyl radical could directly attack the C≡C bond under the Cu(II)/B_2pin_2 catalytic system.[9b]

We commenced our study by using 1-(cyclopropylethynyl)-2-nitrobenzene (**1a**) and $BrCF_2CO_2Et$ (**2a**) as model substrates. To our delight, the desired product **3a** was obtained in 74% yield when $CuCl_2$ (10 mol %)/dtbbpy (**L1**) (10 mol %) was employed in the presence of B_2pin_2 (2.5 equiv) and Na_2CO_3 (2.5 equiv) in 1,4-dioxane (0.1 M) at 100 °C for 12 h, which turned out to be the optimal conditions (Table 1, entry 1). Various alterations were performed to test the influences on the optimal conditions (Table 1). First, lower reactivity was observed when the reaction was conducted under air (entry 2). When we reduced the reaction temperature from 100 to 80 °C, the yield of **3a** was slightly decreased to 73% (entry 3). Only marginal improvements were achieved when other copper salts were employed instead of $CuCl_2$ (entries 4 and 5). Employing a series of other bipyridine ligands (**L2**, **L3**, **L4**) resulted in lower yields of the desired product **3a** (entries 6−8). Regrettably, shortening the reaction time led to a decreased yield of **3a** (entry 9). KF also demonstrated itself as an effective base, giving **3a** in 70% isolated yield (entry 10). Of note, the reactivity was entirely restrained when an organic base such as pyridine was used (entry 11). When the reactions were carried out in the absence of $CuCl_2$ and ligand (entries 12 and 13), no product **3a** was obtained. Solvent screening indicated that 1,4-dioxane was superior to THF and acetonitrile (entries 14 and 15). Reducing the amount of B_2pin_2 decreased the yield of **3a** (entry 16). Among the boron reagents investigated, B_2pin_2 showed the optimal efficiency compared with B_2cat_2 and $B_2(OH)_2$ (entries 17 and 18).

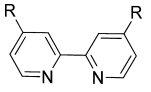
The optimized conditions were used to investigate the substrate scope and reaction parameters. First, we examined the reactions of 2-alkynylnitroarene derivatives **1** with **2a** (Scheme 2). Compared with the 2-cyclopropyl-substituted substrates, 2-phenyl-substituted **1b** exhibited relatively low reactivity, probably as a result of the electron-inductive effect of the phenyl group. Although the R^2 group made a difference in the reactivity, the substituent R^1 on the aromatic ring of the 2-alkynylnitroarene had no distinct influence, and the corresponding 3-oxindoles were obtained in moderate yields (**3c**−**e**). The structure of **3c** was confirmed by X-ray analysis, which analogously signified the texture of product **3**. Noteworthily, product **3f** was obtained in an inferior yield; this result was consistent with our previous report,[12] in which the property of the substituent *para* to the NO_2 group significantly affected the reductive cyclization, with electron-withdrawing groups favor-

Table 1. Optimization of the Reaction Conditions[a]



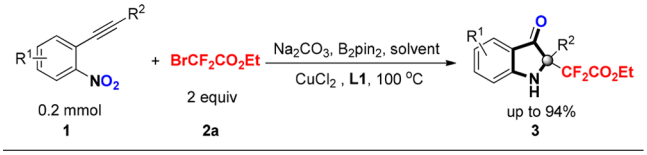
entry	variation from the standard conditions	yield (%)[b]
1	none	78 (74)[c]
2	under air	13
3	at 80 °C	73
4	$CuBr_2$ instead of $CuCl_2$	75
5	$CuF_2·H_2O$ instead of $CuCl_2$	73
6	**L2** instead of **L1**	34
7	**L3** instead of **L1**	46
8	**L4** instead of **L1**	35
9	6 h instead of 12 h	69
10	KF instead of Na_2CO_3	76 (70)[c]
11	pyridine instead of Na_2CO_3	N.R
12	without $CuCl_2$ and **L1**	N.R
13	without ligand	N.R
14	THF instead of 1,4-dioxane	24
15	MeCN instead of 1,4-dioxane	54
16	2 equiv of B_2pin_2	70
17	B_2cat_2 instead of B_2pin_2	trace
18	$B_2(OH)_2$ instead of B_2pin_2	45

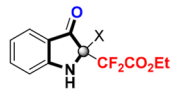
[a]Reaction conditions: **1** (0.2 mmol), $BrCF_2CO_2Et$ (2 equiv), Na_2CO_3 (2.5 equiv), B_2pin_2 (2.5 equiv), $CuCl_2$ (10 mol %), and **L1** (10 mol %) in 1,4-dioxane (0.1 M) at 100 °C for 12 h. [b]Yields were determined by GC analysis. [c]Isolated yield.



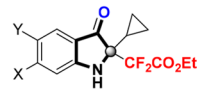
R = *t*Bu, **L1**
R = OMe, **L2**
R = H, **L3**
R = Me, **L4**

Scheme 2. Scope of 2-Alkynylnitroarenes 1[a]

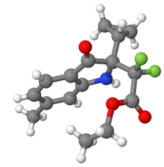




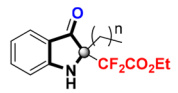
3a, X = cyclopropyl, 74%
3b, X = Ph, 36%



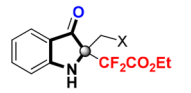
3c, Y = H, X = Me, 53%
3d, Y = H, X = F, 62%
3e, Y = H, X = Cl, 60%
3f, Y = OMe, X = H, 36%[b]



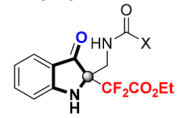
X-ray crystal structure of 3c



3g, n = 2, 55%
3h, n = 3, 51%
3i, n = 4, 45%



3j, X = $(CH_2)_3OH$, 44%
3k, X = OPh, 41%



3l, X = Et, 53%
3m, X = *i*Pr, 72%
3n, X = *t*Bu, 94%

[a]Reaction conditions: **1** (0.2 mmol), $BrCF_2CO_2Et$ (2 equiv), Na_2CO_3 (2.5 equiv), B_2pin_2 (2.5 equiv), $CuCl_2$ (10 mol %), and **L1** (10 mol %) in 1,4-dioxane (0.1 M) at 100 °C for 12 h. [b]**1f** (0.5 mmol), $CuCl_2$ (5 mol %), and **L1** (5 mol %) in 1,4-dioxane (4 mL) at 80 °C.

DOI: 10.1021/acs.orglett.7b03678
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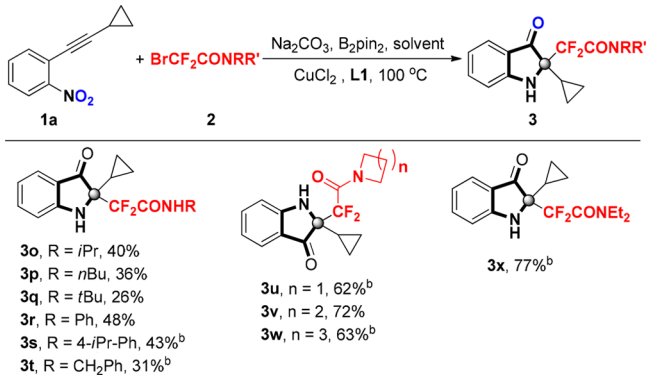
ing the reaction, since the Hammett plot suggested that an anionic or partially anionic moiety was formed during the process. In addition to 2-cyclopropyl substituents, the alkyl-substituted substrates **1g–k** were also amenable to these reaction conditions, rendering the products **3g–k** in moderate yields. It is not surprising that the yields gradually declined in the order of **3g** to **3i**, probably because of increasing steric congestion. To our delight, alcohol and ether were also good substrates in our reactions, rendering the corresponding products **3j** and **3k** in moderate yields. Amides were compatible with our standard conditions as well, and interestingly, the X group in the amide had a significant influence on the efficiency of the reaction: the yield observably increased in the sequence of ethyl < isopropyl < *tert*-butyl substitution on the substrate (**1l**, **1m**, and **1n**), respectively, delivering the products **3l–n** in 53%, 72%, and 94% yield.

Next, we investigated the reactivity of other difluoroalkyl radicals (Scheme 3). Although relatively low conversion was

Scheme 3. Scope of Bromodifluoroalkanes 2[a]

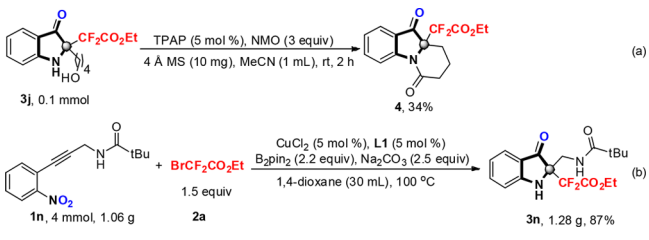


[a]Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv), Na_2CO_3 (2.5 equiv), B_2pin_2 (2.5 equiv), $CuCl_2$ (10 mol %), and **L1** (10 mol %) in 1,4-dioxane (0.1 M) at 100 °C for 12 h. [b]**2** (1.2 equiv).

observed when *N*-monosubstituted difluorobromoacetamides were used as difluoroalkyl reagents (**3o–t**), the *N*,*N*′-disubstituted difluorobromoacetamides were good candidates and delivered the corresponding products in good yields (**3u–x**).

The product **3j** is a valuable compound. When it was subjected to Ley oxidation conditions, the tricyclic compound ethyl 2-(6,10-dioxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indol-9a-yl)-2,2-difluoroacetate (**4**) was obtained in 34% yield (Scheme 4a).[13] To verify the practicality of this protocol, the scaled-up reaction of *N*-(3-(2-nitrophenyl)prop-2-yn-1-yl)-pivalamide (**1n**) (4 mmol, 1.06 g) with **2a** was carried out,

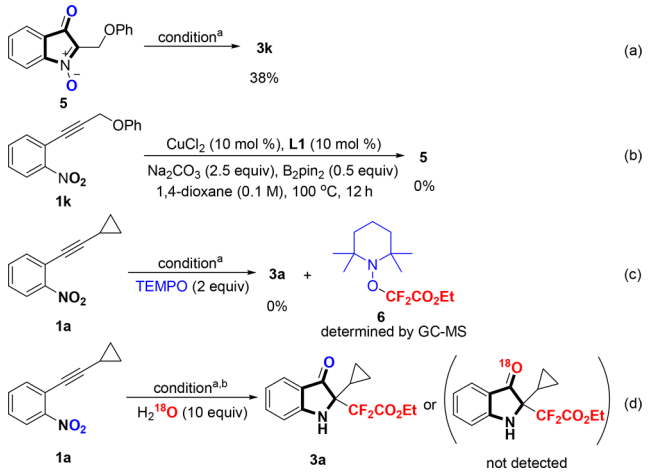
Scheme 4. Further Transformation and Large-Scale Synthesis



and the product **3n** was readily isolated in 87% yield (1.28 g) (Scheme 4b).

In order to acquire further insight into the reaction mechanism, some control experiments were performed. When 3-oxo-2-(phenoxymethyl)-3*H*-indole-1-oxide (**5**) was submitted to the standard conditions, the desired product **3k** was obtained in 38% yield (vs 41% in Scheme 2) (Scheme 5a).

Scheme 5. Control Experiments for Mechanistic Studies



[a]$BrCF_2CO_2Et$ (2 equiv), Na_2CO_3 (2.5 equiv), B_2pin_2 (2.5 equiv), $CuCl_2$ (10 mol %), and **L1** (10 mol %) in 1,4-dioxane (0.1 M) at 100 °C for 12 h. [b]Anhydrous 1,4-dioxane (0.1 M).

Also, isatogen **5** as an ambiguous precursor was not generated when the reaction was performed in the absence of bromodifluoroalkane (Scheme 5b), which implies that the 3-oxo-3*H*-indole-1-oxide compound is not the key intermediate for this transformation. Radical trapping experiments were performed to help in understanding the mechanism. Not surprisingly, this reaction was absolutely suppressed in the presence of TEMPO, and the TEMPO–CF_2CO_2Et complex **6** was detected by GC–MS, indicating that a difluoroalkyl radical is indeed generated in this process (Scheme 5c). To elucidate the origin of the carbonyl oxygen atom of the products, an oxygen-18 labeling experiment was performed. No ^{18}O-labeled **3a** was detected by HRMS when the reaction was conducted in the presence of 10 equiv of $H_2{}^{18}O$, indicating that the carbonyl oxygen atom in the product should be derived from the nitro group rather than H_2O in the solvent (Scheme 5d).

According to our previous work,[9,12] a plausible mechanism for the copper-catalyzed redox cyclizations is described in Scheme 6. Initially, the LCu^IX complex translates into LCu^I–Bpin species **A** with the help of B_2pin_2 and Na_2CO_3. Then **2** is activated by single electron transfer (SET) and reacts with **A** to afford a radical complex, leading to species **C** via **B**. **C** attacks and activates the substrate **1** to give species **D**. Then nitroxide addition to the triple bond of **D** produces **E**, after which redox of **E** affords species **F**.[14] Subsequently, the isatogen structure complex **G** is generated by intramolecular trapping of the nitroso group in 5-exo annulation of **F**,[2,6,7] whereupon, with the help of diboron/base, **G** is transformed to N–O–Bpin species **H**, which undergoes diborane-mediated deoxygenation and reductive elimination of the copper catalyst to deliver the product **3** and regenerates species **A**.

In conclusion, we have disclosed an efficient synthesis of 3-oxindoles via inexpensive copper-catalyzed internal redox

DOI: 10.1021/acs.orglett.7b03678
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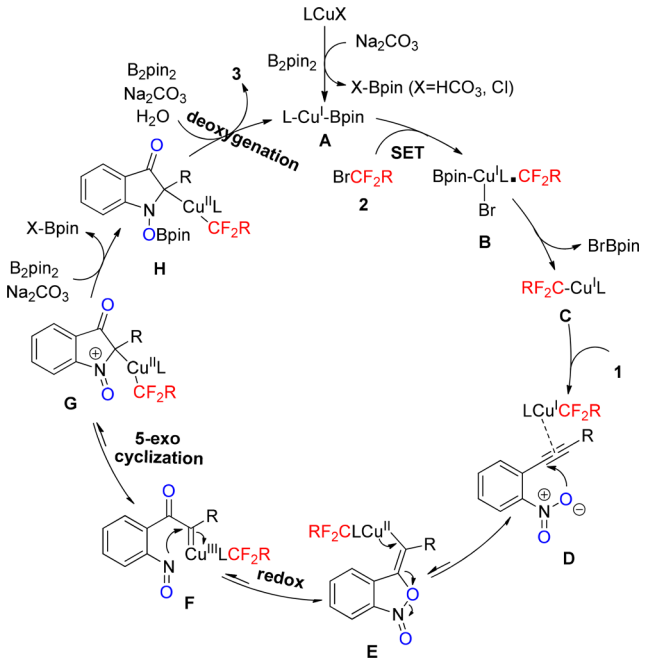
Scheme 6. Plausible Mechanism



cycloisomerization of a non-prefunctionalized nitroalkyne with difluoroalkyl radicals, which provides simple and straightforward access to a wide range of 2,2-disubstituted indolin-3-ones bearing C2 stereocenters. Meanwhile, difluoroalkylation of C2-tetrasubstituted pseudoindoxyls was successfully realized for the first time, rendering fluorine-containing non-carbon quaternary centers in mild to excellent yields using diboron as the reductant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03678.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1570968 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 e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Recruitment Program of Global Experts (1000 Talents Plan), the Natural Science Foundation of Fujian Province (2016J01064), the Fujian Hundred Talents Plan, the Program of Innovative Research Team of Huaqiao University (Z14X0047), and the Subsidized Project for Cultivating Postgraduates' Innovative Ability in Scientific Research of Huaqiao University (for W.F.) is gratefully acknowledged. We also thank the Instrumental Analysis Center of Huaqiao University for analysis support.

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DOI: 10.1021/acs.orglett.7b03678
Org. Lett. XXXX, XXX, XXX−XXX