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Converting *gem*-Dimethyl Groups into Cyclopropanes via Pd-Catalyzed Sequential C–H Activation and Radical Cyclization

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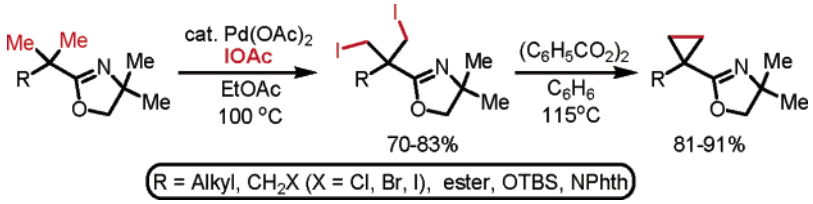
ABSTRACT



A novel route to the synthesis of cyclopropane derivatives is described. 1,1-Dimethyls in 2-(1,1-dimethylalkyl)dimethyloxazolines are first converted into 1,3-diiodide derivatives via Pd-catalyzed sequential C–H activation and then radically cyclized to provide 2-(1-alkylcylcopropyl)-dimethyloxazolines. The use of EtOAc as a solvent is crucial for the diiodination of the functionalized substrates.

Cyclopropanes serve as versatile building blocks in organic synthesis because of their ability to undergo various transformations.[1] The rigid carbocyclic system has been of great value to alter the activity of biologically active compounds by restricting their conformation.[2] Their widespread occurrence in natural products[3] and biologically active analogues[4] has warranted increasing research interests. Therefore, novel approaches to construct them in a variety of molecular backbones would be of considerable significance. Cyclopropanes are commonly synthesized from alkenes by Simmons−Smith and related reactions,[5] transition metal-catalyzed carbene transfer,[6] and Michael-initiated ring closure (MIRC).[7] Recently, more diverse approaches have been sought to synthesize variously functionalized cyclopropane derivatives.[8] However, less attention has been paid to the formation of cyclopropane derivatives from 1,3-dihalides via a radical cyclization. 1,3-Dihalogen derivatives can be reductively cyclized to cyclopropanes by using metal reduc-

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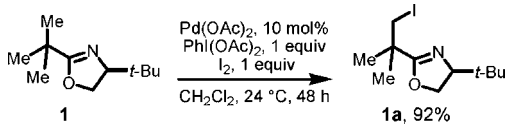
tion,[9] metal−hydride reduction,[9b,c,10] metal−halogen interchange reactions,[11] and metal complexes.[12] Leonard reported a single case of cyclopropanation of 1,3-diiodopropane in quantitative yield using benzoyl peroxide via radical-induced γ-elimination.[13] Although these methods produce excellent yields of cyclopropane derivatives, they have found limited utility in synthesis because of the lack of a general procedure to access the required 1,3-dihalides.[10,14] Herein, we report a novel route to prepare 2,2-disubstituted 1,3-diiodide derivatives from 2-(1,1-dimethylalkyl)dimethyloxazolines via Pd-catalyzed sequential sp^3 C−H activation and subsequent conversion to cyclopropane derivatives by radical cyclization. This protocol provides an unusual conversion of *gem*-dimethyl into cyclopropyl groups in good yields. Remarkably, the diiodination reaction can be carried out in gram-scale quantity and also the catalytic system allows the reuse of the Pd catalyst for at least five times by simply decanting the reaction solution.

We have recently reported the use of oxazoline as the directing group for Pd-catalyzed room temperature monoiodination of sp^3 and sp^2 C−H bonds[15] using IOAc as the terminal oxidant. IOAc generated from the reaction of I_2 with either $PhI(OAc)_2$[16] or AgOAc[17] is a superior oxidant for mild condition C−H functionalization (eqs 1−2). A highly selective monoiodination was achieved by using a sterically bulky chiral group in the oxazoline ring (Scheme 1).

Scheme 1. Pd-Catalyzed Selective Monoiodination



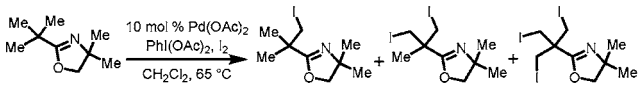
1

$$AgOAc + I_2 \rightarrow AgI + IOAc \quad (1)$$

$$PhI(OAc)_2 + I_2 \rightarrow PhI + IOAc \quad (2)$$

The multistep C−H activation process using a single directing group represents one way of enhancing the practical efficiency of directed C−H activation reactions. In our effort to carry out multistep C−H activation, we rigorously attempted to convert oxazoline **1** to a 1,3-diiodide derivative. Despite the use of high reaction temperature (120 °C) and a surplus amount of the oxidant (3 equiv), the reaction in different solvents such as CH_2Cl_2, DCE, and EtOAc provided the monoiodide as the predominant product. We anticipated that sequential C−H activation could be achieved if a sterically less demanding nonchiral oxazoline was used. We were delighted to find that the diiodide can be obtained as a main product by using 1 equiv of the oxidant ($PhI(OAc)_2$/I_2). Thus, stirring substrate **2** with 10 mol % $Pd(OAc)_2$, 1 equiv of $PhI(OAc)_2$, and 1 equiv of I_2 in CH_2Cl_2 for 2.5 h at 65 °C gave mono- and diiodinated products **2a** and **2b** in 10% and 70% yields, respectively (Table 1). The triiodinated product can also be obtained in excellent yield, albeit requiring much longer reaction time (24 h). Both di- and triiodinated products are easily separable by column chromatography.

Table 1. Pd-Catalyzed Di- and Triiodination of 2-(*tert*-Butyl)dimethyloxazoline[a]



2		2a	2b	2c
$PhI(OAc)_2/I_2$	time	yield[a]	yield[a]	yield[a]
1.0 equiv	2.5 h	10 (16)%	70 (76)%	5 (8)%
2.0 equiv	24 h	0%	2%	90 (98)%

[a] Isolated yields (NMR yields).

The requisite 2-(1,1-dimethylalkyl)dimethyloxazolines were prepared from 2-amino-2-methyl-1-propanol and the corresponding carboxylic acids. Sterically crowded substrates such as *tert*-butyloxazoline **5** and adamantyloxazoline **6** reacted very well to provide diiodides **5a** and **6a** in good yields (Table 2). The diiodination reaction also tolerated primary halogens such as in substrates **7** and **8** giving good yields of diiodides **7a** and **8a**.

However, the reaction ceased to proceed after monoiodination in oxygen- and nitrogen-containing substrates such as **9** and **10.** Very low yield (30%) of diiodinated product **9b** was obtained in methylene chloride even after prolonged reaction time (72 h) at elevated temperature (100 °C) with a surplus amount of $PhI(OAc)/I_2$ (4 equiv each) (Table 3, entry 1). No diiodinated product was formed in DCE. Reactions carried out in benzene and HOAc at 100 °C for 48 h provided low yields of the diiodinated product **9b**.

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(16) For the generation of IOAc in situ from I_2 and $PhI(OAc)_2$, see: (a) Reference 15. (b) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387−3390. (b) Courtneidge, J. L.; Lusztyk, J.; Pagé, D. *Tetrahedron Lett.* **1994**, *35*, 1003−1006.

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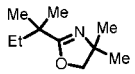
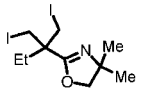
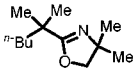
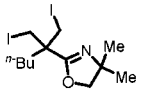
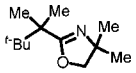
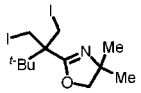
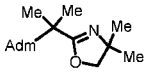
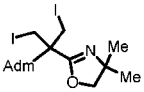
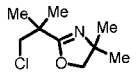
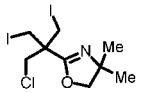
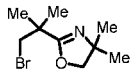
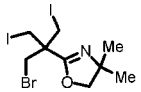
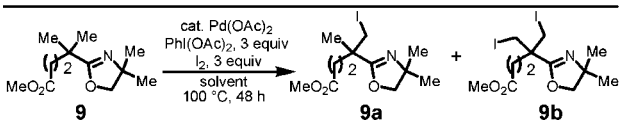
Table 2. Pd-Catalyzed Diiodination of 2-(1,1-Dimethylalkyl)dimethyloxazolines[a]

entry	substrate		product		yield%[b]
1		**3**		**3a**	80 (90)[c]
2		**4**		**4a**	83 (95)
3		**5**		**5a**	80 (88)
4		**6**		**6a**	75 (85)
5		**7**		**7a**	70 (80)
6		**8**		**8a**	73 (85)

[a] Reagents and conditions: 10 mol % $Pd(OAc)_2$, 1−3 equiv of $PhI(OAc)_2$ and I_2, CH_2Cl_2, 65 °C, 24−48 h. [b] Isolated yields (NMR yields). [c] 30 mmol scale reaction.

Reactions attempted in other solvents such as toluene, DMF, MeCN, and NMP proved futile as no iodinated product was observed.

Table 3. Solvent Screening for Diiodination Reaction[a]



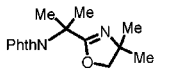
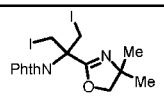
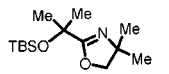
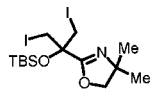
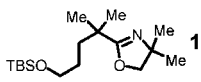
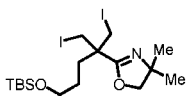
9 **9a** **9b**

entry	solvent	yield%[b]	yield%[b]
1	CH_2Cl_2	10	30[c]
2	DCE	10	0
3	C_6H_6	30	15
4	Toluene	0	0
5	MeCN	0	0
6	^{t}BuOAc	5	82
7	EtOAc	5	83[d]
8	HOAc	5	40
9	NMP	0	0
10	DMF	0	0

[a] Reagents and conditions: 2 equiv of $PhI(OAc)_2/I_2$ at 0 h and 1 equiv at 24 h. [b] Isolated yields. [c] 72 h, 4 equiv of $PhI(OAc)_2/I_2$. [d] 5 mmol scale reaction.

Remarkably, the reaction carried out in EtOAc or ^{t}BuOAc produced the diiodinated product in good yields. Thus, stirring a mixture of substrate **9**, 10 mol % $Pd(OAc)_2$, and $PhI(OAc)_2/I_2$ (2 equiv each at 0 h, 1 equiv each at 24 h) in EtOAc at 100 °C for 48 h gave the diiodinated product **9b** in 83% isolated yield. This new iodination procedure displayed a better functional group tolerance. Substrates such as phthalimide-protected α-amino- and TBS-protected α-hydroxy oxazolines **10** and **11** respectively could be diiodinated in good yields (Table 4). Interestingly, nonfunctionalized

Table 4. Pd-Catalyzed Diiodination of 2-(1,1-Dimethylalkyl)dimethyloxazolines Containing Ether and Imide Functionalities[a]

entry	substrate		product		yield%[b]
1		**10**		**10a**	73 (80)[c]
2		**11**		**11a**	79 (85)
3		**12**		**12a**	77 (86)

[a] Reagents and conditions: 10 mol % $Pd(OAc)_2$, 3 equiv of $PhI(OAc)_2$ and I_2, EtOAc, 100 °C, 48 h. [b] Isolated yields (NMR yields). [c] 115 °C, 72 h. Contains ca. 10% monoiodide as an impurity and the given NMR and isolated yields refer to diiodide **10a** only.

substrates **2**−**6** and halogen-containing substrates **7** and **8** gave lower yields of the corresponding diiodinated products in EtOAc in comparison to the reactions carried out in CH_2Cl_2 (see the Supporting Information).

A clear advantage of this catalytic system is that the reaction can be carried out in gram-scale quantity (5.08 g, 30 mmol, substrate **3**) and the palladium catalyst can be easily recycled (Table 5). As PdI_2 precipitates from the solution

Table 5. Recycling Experiment with Substrate **3**[a]

run	1	2	3	4	5
yield (%)[b]	80	76	78	75	76

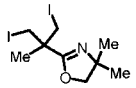
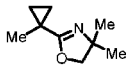
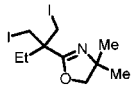
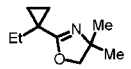
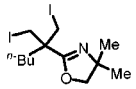
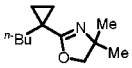
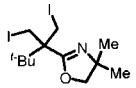
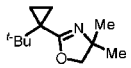
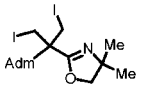
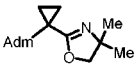
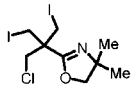
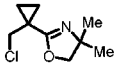
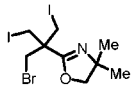
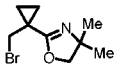
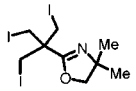
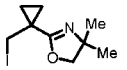
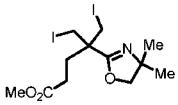
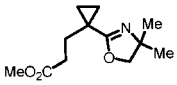
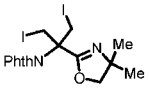
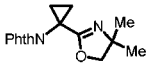
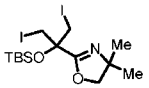
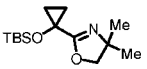
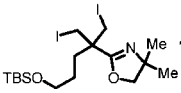
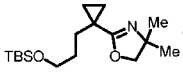
[a] Reagents and conditions: 10 mol % $Pd(OAc)_2$, 2 equiv of $PhI(OAc)_2$ and I_2, CH_2Cl_2, 65 °C, 24 h. [b] Isolated yields.

toward the completion of reaction, it can be isolated by centrifugation and reused for the next run using the same amount of oxidant. With substrate **3**, five runs of diiodination reaction (10 mmol each run) starting with only 0.224 g (10 mol %) of $Pd(OAc)_2$ produced 16.2 g (38.5 mmol) of the diiodinated product **3a**.

With variously functionalized 2,2-disubstituted 1,3-diiodide derivatives in hand, we proceeded to test the feasibility of using Leonard's procedure to radically carbocyclize the

diiodides into cycloproanes.[18] Heating a stirred solution of diiodide **2b** and benzoyl peroxide (2 equiv) in benzene at 115 °C for 2 h produced 1-methylcyclopropane oxazoline **2d** in quantitative yield by NMR (Table 6).

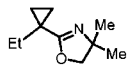
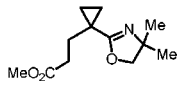
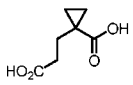
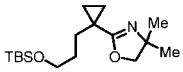
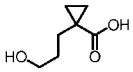
Table 6. Radical Cyclization of 2,2-Disubstituted 1,3-Diiodides[a]

entry	substrate		product		yield%[b]
1		**2b**		**2d**	82
2		**3a**		**3b**	85
3		**4a**		**4b**	90
4		**5a**		**5b**	89
5		**6a**		**6b**	91
6		**7a**		**7b**	81
7		**8a**		**8b**	83
8		**2c**		**2e**	82[c]
9		**9b**		**9c**	90
10		**10a**		**10b**	86
11		**11a**		**11b**	84
12		**12a**		**12b**	85

[a] Reagents and conditions: 2 equiv of benzoyl peroxide, C_6H_6, 115 °C, 2 h. [b] Isolated yields. Substrates are quantitatively converted into the cyclopropane products as measured by ^{1}H NMR. [c] Contains ca. 8% benzoyl peroxide as an impurity and the given NMR and isolated yields refer to diiodide **2e** only.

Halogen (Cl, Br)-containing substrates **7a** and **8a** were selectively cyclized only at the carbons containing iodide substituents. It is interesting to note that the iodide substituent in the triiodide substrate **2c** remained intact as neither a benzoylated nor hydroxylated cyclopropane derivative was detected. The procedure was also compatible with an ester substrate **9b**, TBS-protected hydroxy substrates **11a** and **12a**, and phthalimide-protected α-amino substrate **10a**.[19] The facile hydrolysis of nonfunctionalized and functionalized cyclopropane oxazolines **3b**, **9c**, and **12b** to the corresponding cyclopropanecarboxylic acids (Table 7) in high yields

Table 7. Hydrolysis of Cyclopropapane Oxazolines[a]

entry	substrate		product		yield%[b]
1		**3b**		**3c**	92
2		**9c**		**9d**	85
3		**12b**		**12c**	80

[a] Reagents and conditions: 4 N H_2SO_4:dioxane (1:1), 100 °C, 15 h. [b] Isolated yields.

demonstrates the practicality of the current cyclopropanation protocol.

In summary, we have developed a novel protocol to access 1,3-diiodide and cyclopropane carboxylic acid derivatives via Pd-catalyzed sequential sp^3 C−H activation and radical cyclization. The newly developed protocol provides an efficient route to prepare variously functionalized 2,2-disubstituted 1,3-diiodides and a unique procedure to construct cyclopropane building blocks from readily available α,α-dimethylcarboxylic acids. Moreover, the diiodination reaction can be carried out in gram-scale quantity and the catalyst can be readily recycled.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Reactions of substrates **6a**, **9b**, and **11a** with Zn powder in refluxing ethanol did not produce the corresponding cyclopropanes (see ref 9a).

(19) For recent publications to prepare aminocyclopropanecarboxylic acid derivatives, see: (a)Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433−9440. (b) Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M. A. *Org. Lett.* **2002**, *4*, 4273−4276. (c) Zhao, Z.; Liu, H.-w. *J. Org. Chem.* **2002**, *67*, 2509−2514.