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Assembly of Indoline-2-carboxylate-Embodied Dipeptides via Pd-Catalyzed C(sp^2)−H Bond Direct Functionalization

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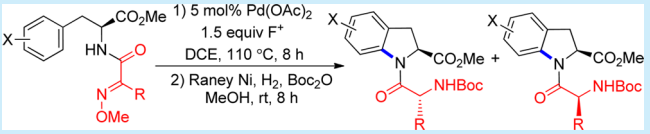
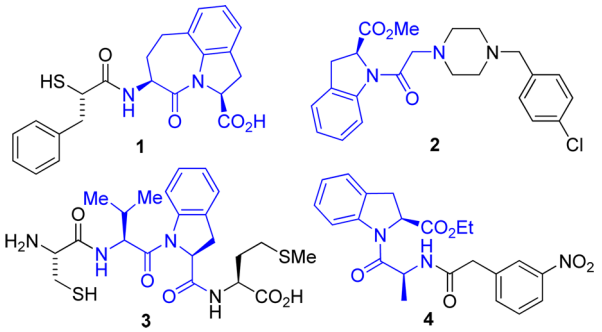
Supporting Information

ABSTRACT: Intramolecular dehydrogenative cyclization of 2-methoxyiminoacyl-protected phenylalanine derivatives proceeded at 110 °C under catalysis of $Pd(OAc)_2$ in the presence of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate to afford substituted indoline-2-carboxylates that were converted into indoline-2-carboxylate-embodied dipeptides via Raney Ni-catalyzed hydrogenation.



Peptidomimetics containing the indoline-2-carboxylate moiety have been found to have a variety of biological activities,[1] including inhibiting zinc metalloproteases angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP)[2] that was displayed by tripeptide **1** (Scheme 1, IC_{50} = 13 nM and 50 nM respectively);[1a] antagonizing dopamine D_2/D_4 receptor demonstrated by dipeptide **2**;[1b] blocking the activity of farnesyltransferase (FT) shown by tetrapeptide **3** (IC_{50} = 37 nM;)[1c] and inhibiting β-amyloid peptide release exhibited by dipeptide **4**.[1d,e] Therefore, developing new synthetic methodologies that allow efficient and convenient assembly of indoline-2-carboxylate-embodied peptidomimetics has been an important goal in recent years.[3]

Scheme 1. Bioactive Peptidomimetics Containing an Indoline-2-carboxylate Moiety



Recent progress in transition-metal-catalyzed C(sp^2)−H bond functionalization[4] has provided an alternative approach for assembling substituted indoline-2-carboxylates in which the key transformation is a palladium-catalyzed aerobic intramolecular dehydrogenative cyclization of phenylalanine derivatives through C(sp^2)−H functionalization.[3b,c,f] It was reported that amine protecting groups play a key role for this transformation because the corresponding amides can serve as directing groups to facilitate C−H cleavage for C(sp^2)−H functionalization. In 2005, palladium-catalyzed arylation of amine derivatives employing aminoquinoline and picolinamide auxiliary as the directing group was disclosed by Daugulis and co-workers.[5] Until now, (trifluoromethyl)sulfonyl, picolinamides, and 2-pyridylsulfonyl have been proven to be suitable protecting groups for this purpose. However, after intramolecular dehydrogenative cyclization, they must be removed for further conversions to prepare useful molecules.

In 2013, we reported that 2-methoxyiminoacyl (MIA) was a powerful amine auxiliary for palladium-catalyzed direct γ-arylation of 2-aminobutanoic acid derivatives.[6] The amine auxiliary in resultant γ-arylation products **6** could be easily removed under mild conditions to provide protected amino acids **7** or converted into dipeptides **8** via simple hydrogenation (Scheme 2). In order to further explore the synthetic usage of this amine auxiliary, we attempted palladium-catalyzed aerobic intramolecular dehydrogenative cyclization of 2-methoxyiminoacyl-protected phenylalanines **9** and were pleased that the C−H amination proceeded smoothly under the catalysis of $Pd(OAc)_2$ to afford the substituted indoline-2-carboxylates **10**, which could be transformed into indoline-2-carboxylate-embodied dipeptides **11** and **12** upon hydrogenation. Herein, we disclose our results.

As indicated in Table 1, we chose amide **9a** as a model substrate for exploring suitable cyclization conditions. Under the catalysis of 10 mol % of $Pd(OAc)_2$, the reaction took place at 110 °C and in the presence of 2.0 equiv of $PhI(OAc)_2$, providing the desired cyclization product **10a** in 30% yield, together with overoxidized product[3d,7] **13a** in 28% yield (entry

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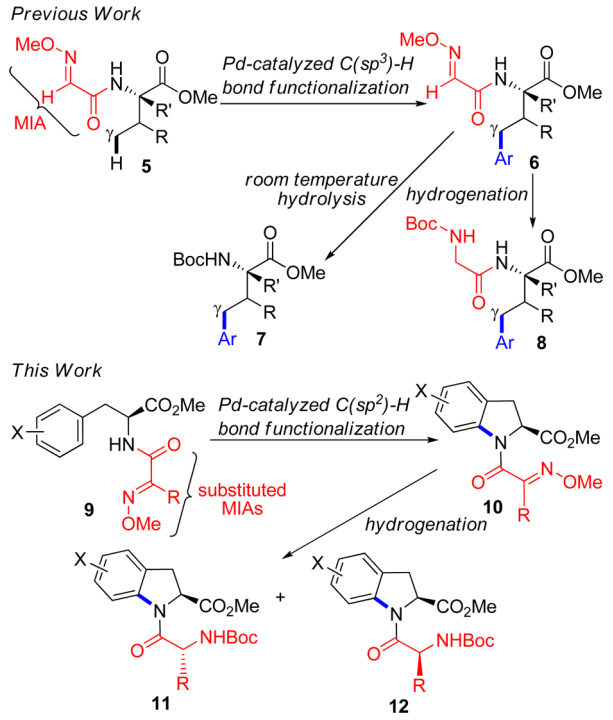
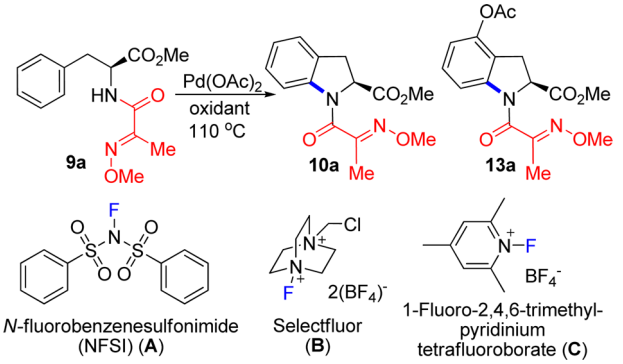
Scheme 2. Synthesis of Dipeptides via Pd-Catalyzed C(sp^3)–H and C(sp^2)–H Bond Functionalization



1). Little improvement was observed when reaction was carried out at an argon atmosphere or using acetic anhydride as the solvent (entries 2 and 3). Changing the oxidant to $K_2S_2O_8$[6,8] and $Ce(SO_4)_2$[3b] resulted in no or poor conversion (entries 4 and 5). In light of recent developments using bystanding F^+ oxidants to promote selective reductive elimination of high-valent metal centers,[9] we examined several F^+ (**A**–**C**) sources[10] as the oxidants and were pleased that overoxidization could be avoided and F^+(**C**) could give the cyclization product in a satisfactory yield (entries 6–8). In this case, addition of 1.25 equiv of DMF was crucial to ensure good conversion.[3b] The reaction proceeded more efficiently under an argon atmosphere (compare entries 8 and 9), indicating that oxygen has some inhibitory effect to the present transformation. Reducing the loading of F^+(**C**) from 2 equiv to 1.5 equiv did not alter the reaction yield; however, further reduction decreased the reaction yield significantly (entries 9–11). Interestingly, reducing the catalyst loading even gave better results (entries 12 and 13), and the best result (86% yield) was obtained when 5 mol % of $Pd(OAc)_2$ and 1.5 equiv of F^+(**C**) were adopted (compare entry 14 with entries 9–13). More importantly, the high enantiopurity of the cyclization product **10a** (97% ee) indicated that no racemization occurred during the reaction course. Additionally, further reduction of the loading of $Pd(OAc)_2$ and F^+(**C**) resulted in incomplete conversion, leading to decreased yields (entries 15 and 16).

With the optimal reaction conditions in hand, we next examined the reaction scope by varying the directing groups and the substituents on the aromatic ring of phenylalanines, and the results are summarized in Scheme 3. It was found that three other directing groups also worked well, leading to the formation of **10b–d** in 78–86% yields. Further investigations revealed that a wide range of phenylalanine derivatives bearing either electron-donating or electron-withdrawing groups were compatible with this C–H functionalization protocol, thus

Table 1. $Pd(OAc)_2$-Catalyzed Intramolecular Dehydrogenative Cyclization of Amide 9a



entry	$Pd(OAc)_2$ (mol %)	additives/atm	solvent	time (h)	yield (%) 10a[a]	yield (%) 13a
1	10	2.0 equiv of $PhI(OAc)_2$, air	PhMe	16	30	28
2	10	2.0 equiv of $PhI(OAc)_2$, Ar	PhMe	16	32	26
3	10	2.0 equiv of $PhI(OAc)_2$, Ar	Ac_2O	2	35	32[b]
4	10	2.0 equiv of $K_2S_2O_8$, air	PhMe	16	<1	
5	10	2.0 equiv of $Ce(SO_4)_2$, air	DCE	16	30	
6[c]	10	2.0 equiv of F^+(**A**), air	DCE	16	<1	
7[c]	10	2.0 equiv of F^+(**B**), air	DCE	16	48	
8[c]	10	2.0 equiv of F^+(**C**), air	DCE	16	65	
9[c]	10	2.0 equiv of F^+(**C**), Ar	DCE	8	73	
10[c]	10	1.5 equiv of F^+(**C**), Ar	DCE	8	74	
11[c]	10	1.0 equiv of F^+(**C**), Ar	DCE	8	65	
12[c]	5	2.0 equiv of F^+(**C**), Ar	DCE	8	80	
13[c]	2	2.0 equiv of F^+(**C**), Ar	DCE	8	77	
14[c]	5	1.5 equiv of F^+(**C**), Ar	DCE	8	**86 (88)**[b]	
15[c]	5	1.2 equiv of F^+(**C**), Ar	DCE	8	80	
16[c]	2	1.5 equiv of F^+(**C**), Ar	DCE	8	73	

[a]Yields are based on ^1H NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as an internal standard on a 0.1 mmol scale. [b]Yields based on isolated products on a 0.5 mmol scale. [c]With 1.25 equiv of DMF.

giving the corresponding cyclization products in good to excellent yields. Interestingly, the yield of a substrate possessing forced electron-donating functional group OBn (**10i**) was relatively low, and the corresponding indole products were isolated in 12% yield, while similar overoxidation was not observed for substrates with an OTf or OAc group (**10g** and **10h**). It is noteworthy that some functional groups such as OAc, OTf, nitro, and halogens including chloro, bromo, and even iodo were preserved under these reaction conditions. Furthermore, the orientation of substituents has a weak

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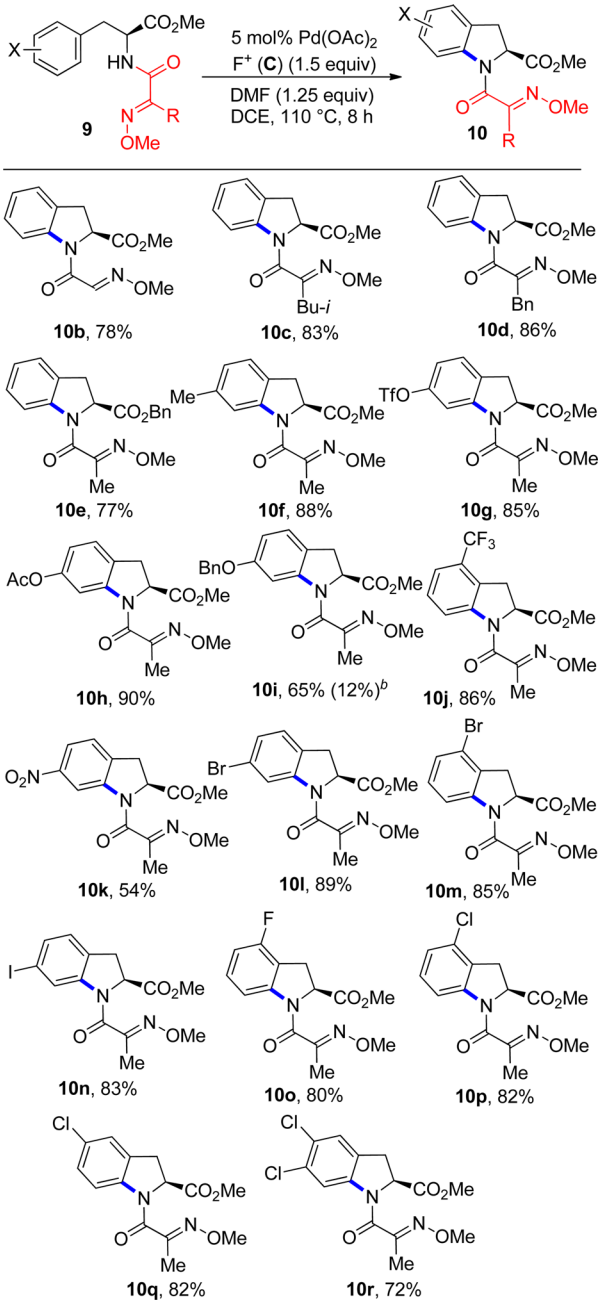
Scheme 3. Synthesis of Substituted Indoline-2-carboxylate via Pd-Catalyzed Direct Amination[a]

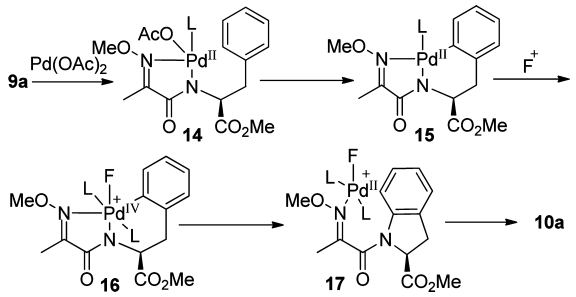


[a]Yields based on isolated products on a 0.5 mmol scale. [b]Corresponding indole product was isolated in 12% yield.

influence on the reactivity (compare **10l** with **10m** and **10q** with **10p**). This unique combination of reactivity and functional group compatibility provided a convenient and efficient route for the formation of various chiral indoline-2-carboxylates. In addition, the structure of **10p** was unambiguously confirmed by X-ray diffraction crystallography.

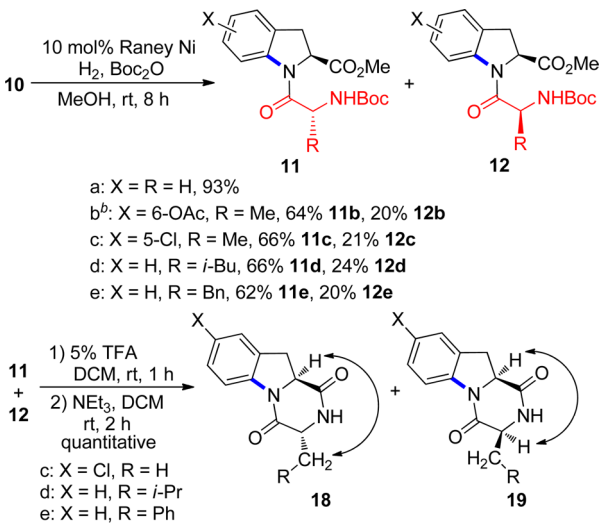
Although a detailed mechanistic investigation of the present amination process awaits further experimental evaluation, our tentative hypothesis is outlined in Scheme 4. Based on the studies by the Ritter[9c,e] and Yu[3b] groups, we speculated that the amide **9a** might react with a Pd(II) species to form the palladium amidate **14** and therefore facilitate a subsequent C–H insertion to give the double palladium chelate **15**. After an oxidative process of the two-electron oxidant (F^+), the resultant complex **16** with a Pd(IV) center[11] undergoes reductive elimination to deliver the product **10a** through the intermediate **17**. Noteworthy is that for this transformation a mechanism via Pd(III) intermediate[12,13] is also possible.

Scheme 4. Possible Reaction Mechanism



To demonstrate the synthetic usage of the present cyclization reaction, we attempted further transformations of the cyclization products **10**. To our delight, hydrogenation of the oxime moiety in **10b** proceeded smoothly under the catalysis of Raney Ni at ordinary pressure and temperature to afford dipeptide **11a** in 93% yield after protection with Boc anhydride (Scheme 5). For other substrates, a new chiral center was created after hydrogenation, leading to formation of two diastereoisomers that could be easily separated by column chromatography. There is a moderate asymmetric induction during hydrogenation as about 3:1 diastereomeric ratio for **11** and **12** were observed. To determine the relative stereochemistry of the diastereomers, we removed the Boc protecting group in **11** and **12** and then treated then with triethylamine to deliver tricyclic compounds **18** and **19**, whose structures were established by NOESY studies.

Scheme 5. Transformation into the Boc-Protected Dipeptides[a]



[a]Isolated yield. [b]Solvent: 20% THF in MeOH.

In summary, we have developed an effective protocol for the synthesis of dipeptides containing indoline-2-carboxylate via palladium-catalyzed direct amination of phenylalanine derivatives. The key for this success is employing substituted

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methoxyiminoacyl (MIA) as the directing groups and a F^+ source as the oxidant. This method features high efficiency and wide functional group tolerance. Applications of these directing groups to other coupling reactions, together with detailed mechanistic studies, are being explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectra data and copies of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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