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Auxiliary-Directed Pd-Catalyzed γ-C(sp^3)−H Bond Activation of α-Aminobutanoic Acid Derivatives

Kalyan Kumar Pasunooti, Biplab Banerjee, Terence Yap, Yaojia Jiang, and Chuan-Fa Liu*

School of Biological Sciences, Nanyang Technological University, Singapore 637551

Supporting Information

ABSTRACT: New bidentate auxiliaries derived from the isoxazole-3-carboxamide and oxazole-4-carboxamide moieties were used for Pd-catalyzed C(sp^3)−H bond activation. The results show that, when placed on a primary amine compound, 5-methylisoxazole-3-carboxamide (MICA) directs Pd-catalyzed activation of inert γ-C(sp^3)−H bonds for C−C bond formation. Selective and efficient arylation and alkylation of several α-aminobutanoic acid derivatives led to various γ-substituted non-natural amino acids. The MICA directing group can be conveniently removed and recovered under very mild conditions.

Transition-metal-catalyzed direct functionalization of C−H bonds has been an area of intensive research in recent years.[1] A main objective is to achieve selective activation of one particular C−H bond in the presence of many similar ones. The most common strategy involves the use of directing groups that can present the metal catalyst to a proximal carbon atom via the formation of a metallacyclic intermediate.[2] Compared to the extensively studied direct functionalization of C(sp^2)−H bonds,[3] site-selective activation of inert aliphatic C(sp^3)−H bonds is more challenging.[4] Both monodentate and bidentate groups have been developed to direct C(sp^3)−H bond activation, many of which can be removed post functionalization.[5−14] Of the bidentate directing groups, the carboxamide formed from 8-aminoquinoline (AQ) was first developed by Daugulis et al. for the β arylation of carboxylic acid derivatives using aryl iodide reagents and palladium acetate catalyst.[8a] Corey[8b] and Daugulis[8d] successfully used this method to prepare non-natural amino acids through Pd-catalyzed C−C and C−O bond formation. A number of other amide-based bidentate auxiliaries have subsequently been developed by various research groups for β-C(sp^3)−H functionalization of carboxylic acid derivatives.[8b,9] There has also been parallel development of bidentate auxiliaries for C(sp^3)−H functionalization of amine compounds.[8a,10−14] Of these auxiliaries, three have been shown to be useful for the arylation/alkylation of inert γ-C(sp^3)−H bonds in α-aminobutanoic acid derivatives (Figure 1). This was first demonstrated by Chen's group[10] using the picolinamide (PA) directing group originally described by Daugulis[8a] and a further designed OTBS-tethered PA auxiliary, which can be removed more easily from the functionalized amino acid analogues under acidic conditions.[10] Carretero et al. reported the use of *N*-(2-pyridyl)sulfonyl auxiliary for the γ-arylation of the amino acid derivatives.[11] Although this directing group can be removed under mild reaction conditions, the C−H arylation step requires high

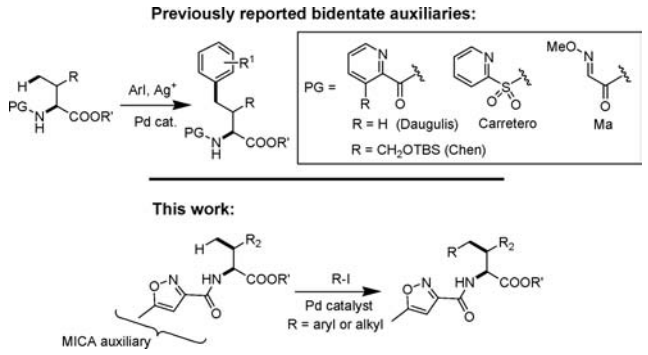

Figure 1. Bidentate directing groups for Pd-catalyzed arylation/alkylation of γ-C(sp^3)−H bond of α-aminobutanoic acids.

reaction temperatures (150 °C). In 2013, Ma's group developed the methoxyiminoacetyl (MIA) directing group for γ-C(sp^3)−H functionalization of α-aminobutanoic acid derivatives.[12] The MIA group is structurally simple and can be easily prepared in a few synthetic steps. It can be easily removed under basic conditions by treatment with 1 N KOH.

We hypothesized that the isoxazole-3-carboxamide and oxazole-4-carboxamide moieties might provide a new type of scaffolds for bidentate chelating with the Pd ion for γ-C(sp^3)−H activation shown in Figure 1. In this study, we have indeed found two efficient auxiliaries of this type that operate under mild conditions (60−80 °C). Several unsubstituted and substituted isoxazole-3-carboxylic acids and oxazole-4-carboxylic acids are commercially available. We have chosen four of them to form the amides with an amine for this study (Table 1).

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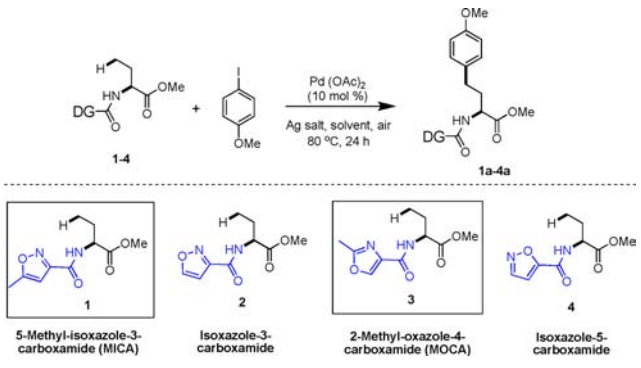
Table 1. Screening of New Auxiliaries and Optimization of Reaction Conditions for MICA-Directed γ-Arylation[a]



entry[a]	substrate	solvent	Ag salt,[c] additive	yield[d] (%)
1	**1**	HFIP	AgOAc	18 + recovd **1**
2	**1**	DCE	AgOAc	26 + recovd **1**
3	**1**	**toluene**	**AgOAc**	**91**
4[b]	**1**	toluene	Ag_2CO_3	no reaction
5[b]	**1**	toluene	AgTFA	no reaction
6[b]	**1**	toluene	Cs_2CO_3	no reaction[d]
7	**1**	toluene	AgOAc, PivOH[e]	78
8	**2**	toluene	AgOAc	35, dec
9	**3**	**toluene**	**AgOAc**	**83**
10[b]	**4**	toluene	AgOAc	no reaction

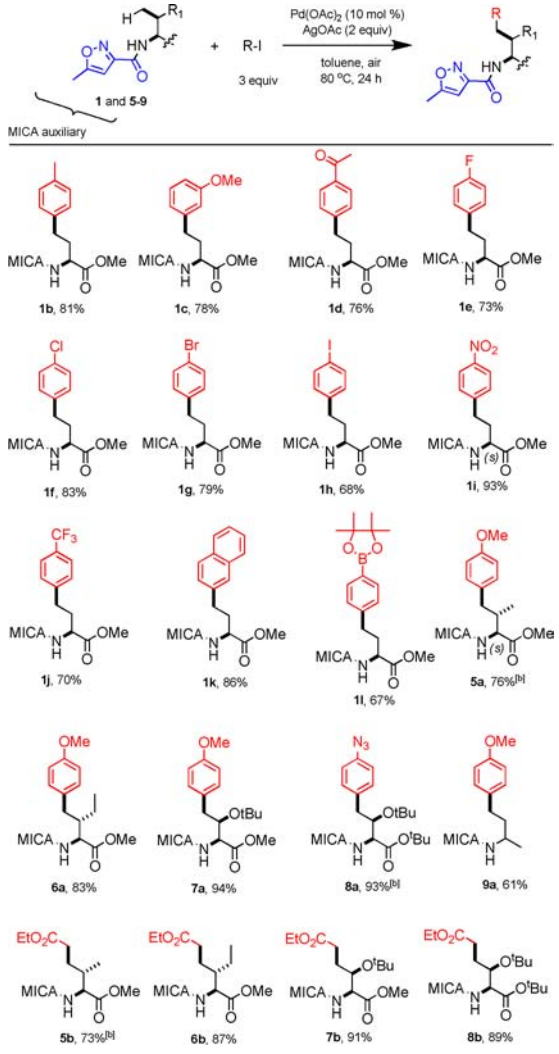
[a]All of the screening reactions were carried out in a Teflon cap sealed tube on 0.22 mmol scale of the substrate at 0.5 M concentration. [b]Recovered starting material. [c]2 equiv of Ag^+ salt. [d]Yield of isolated product after column chromatography. [e]1 equiv of additive. HFIP = hexafluoroisopropanol, DCE = dichloroethane, Piv = pivaloyl, AgTFA = silver trifluoroacetate.

We started our investigation with the 5-methylisoxazole-3-carboxamide (MICA) auxiliary. The arylation of **1** with 4-iodoanisole was used as a model reaction (Table 1). The solvent system has a profound effect on the Pd-catalyzed reaction (entries 1−3). When HFIP or DCE was used as the solvent (entry 1 and 2), the product was formed in very low yields and the remaining substrate was recovered. On the other hand, toluene was an excellent solvent (entry 3). This finding is interesting considering that, for Ma's MIA directing group which also has an O−N bond, HFIP was the preferred solvent while toluene gave poor yields. Silver acetate was the best iodide quencher (entry 3); however, silver carbonate and silver trifluoroacetate did not provide any desired product (entries 4 and 5), nor did Cs_2CO_3 (entry 6). In these cases, starting material **1** was recovered (entries 4−6). The addition of PivOH as an additive did not help (entry 7). So when compound **1** was treated with 4-iodoanisole (3 equiv), 10 mol % of $Pd(OAc)_2$, and AgOAc (2 equiv) in toluene at 80 °C for 24 h, a near-complete conversion to the product **1a** was observed with 91% isolated yield (entry 3).

We next tested isoxazole-4-carboxamide (ICA) (**2**), 2-methyloxazole-4-carboxamide (**3**), and isoxazole-5-carboxamide (**4**) auxiliaries in the same γ-arylation reaction (Table 1). Surprisingly, the unsubstituted isoxazole-4-carboxamide (ICA) auxiliary gave a poor yield of only ca. 35% of the desired product. In this case, the starting material was completely consumed, but unexpected decomposition reactions involving the isoxazole ring occurred. Thus, the methyl group at the 5-position of the isoxazole ring seems to be crucial for the MICA auxiliary to have the stability and balanced electron distribution for chelating with the metal in this reaction. Similarly to MICA, 2-methyloxazole-4-carboxamide (MOCA) (**3**) was also a very good auxiliary (entry 9). In contrast, the isoxazole-5-carboxamide (**4**) auxiliary did not lead to any product and the starting material was recovered after 24 h at 80 °C (entry10). This also proves that the isoxazole oxygen atom and the amide N in **4** are unable to form a productive bidentate auxiliary for chelating with the Pd ion. This screening study establishes MICA and MOCA as effective bidentate directing groups in the test system. On cost considerations, we chose MICA for subsequent studies.

Having found suitable reaction conditions, we proceeded to study the reactivity scope of aryl iodides in the Pd-catalyzed MICA-directed reaction (Table 2). To our delight, aryl iodides bearing a wide range of substitutions, such as methyl, methoxy, acetyl, fluoro, chloro, bromo, iodo, trifluoromethyl, and nitro, provided the desired arylated products in good to excellent yields. Aryl iodides bearing the electron-donating methyl and methoxy groups provided very good yields (**1a−c**). The ketone group from the electron-withdrawing acetyl substituent was

Table 2. Substrate Scope for MICA-Directed γ C−H Functionalization with Aryl Iodides and Ethyl Iodoacetate[a,b]



[a]All of the screening reactions were carried out in a Teflon cap sealed tube on a 0.22 mmol scale. [b]Reaction was carried out at 60 °C for 36 h.

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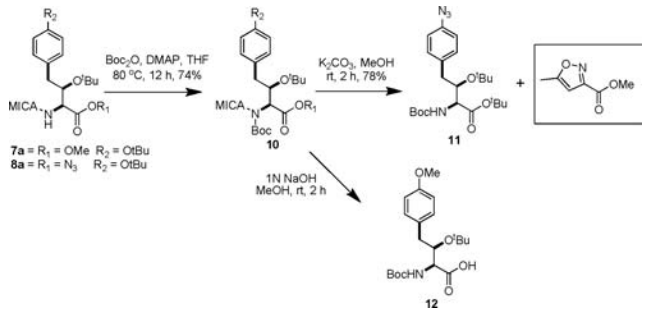
also compatible with the reaction conditions (**1d**). The presence of other halogens (fluoro, chloro, and bromo) in the aryl iodides was also tolerated under the reaction conditions, affording the desired product in excellent yields (**1e**−**g**). Even the presence of another iodide did not significantly affect the reaction (**1h**). Aryl iodides bearing strong electron-withdrawing groups (−NO_2, −CF_3) also gave very good results (**1i** and **1j**); so did the bulky naphthalene iodide (**1k**). The pinacoborane-bearing phenyl iodide was also well tolerated and gave an excellent yield of the desired product (**1l**). The presence of halogen atoms and pinacoborane in the aryl ring of the products (**1f**−**h**,**l**)) opens the door for further functionalization of the products through cross-coupling reactions.

We then extended this methodology to several other natural amino acids. MICA-protected L-valine, L-isoleucine, and L-threonine methyl esters were prepared and subjected to the palladium-catalyzed reaction (Table 2). Arylation with 4-iodoanisole furnished the desired products in good to excellent yields with full conservation of the chiral integrity. Arylation of L-valine derivative **5** with 4-iodoanisole provided predominantly the mono-γ-arylated product **5a** in good yield under very mild conditions (60 °C, 36 h), while giving 15% biarylated product. Interestingly, the L-valine monoarylated product was isolated as a single diastereomer **5a** formed by activating the pro-*S* methyl. This could also provide an opportunity for the sequential diarylation of valine. Based on the previous mechanistic studies[8−12] of C(sp^3)−H functionalization using bidentate directing groups, we believe that the MICA-directed reaction also proceeds via the formation of a stable metallacycle. The high diastereoselectivity observed is likely because the coordination by the isoxazole moiety promotes the formation of a less sterically hindered *trans*-palladacycle that generates the product with the preferred erythro stereochemistry in the valine derivative. For isoleucine, arylation occurred exclusively on the primary γ-sp^3-C (**6a**). For threonine, the presence of the bulky β-*tert*-butoxy group did not hinder the arylation reaction, as the desired products were obtained in excellent yields (**7a** and **8a**). For MICA-protected 2-butylamine **9**, a non-amino acid substrate, reaction with 4-iodoanisole afforded the product (**9a**) in 61% yield. In Ma's MIA-protected 2-butylamine, the same arylation reaction gave the product in only 38% yield.[12] This indicates that MICA is comparatively a more efficient bidentate directing group.

After successful demonstration of MICA-directed γ-arylation with aryl iodides, we decided to test the feasibility of alkylation with these substrates (Table 2, last row). We were gratified to see that reaction of the methyl ester substrates of valine, isoleucine, and threonine (**5**−**7**) with ethyl iodoacetate provided a clean conversion to the alkylated products (**5b**−**7b**). For the valine derivative, the same stereoselectivity was observed (**5b**). The *tert*-butyl ester of MICA-protected threonine (**8**) was also conveniently converted to the alkylated product in 89% yield (**8b**). The alkylation of L-isoleucine methyl ester substrate selectively occurred on the primary γ-CH_3 to provide the product (**6b**) in 87% yield. The arylation and alkylation products (**7a**, **7b**, **8a**, and **8b**) of L-threonine esters would enable the preparation of structurally interesting β-hydroxy amino acids, which are found in many natural products. Previously, Chen's group conducted extensive studies on Pd-catalyzed picolinamide-directed alkylation of unactivated C(sp^3)−H bonds with alkyl iodides.[10b]

We also designed a convenient protocol to remove the MICA directing group after the C−H functionalization (Scheme 1). For example, **7a** or **8a** was treated with $(Boc)_2O$

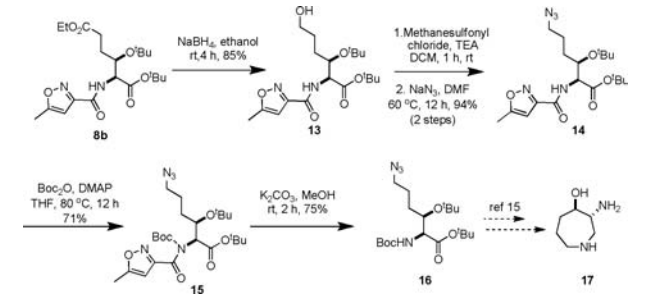
Scheme 1. Removal of DG from the Functionalized Product



in the presence of DMAP to obtain compound **10**. Subsequent treatment of the *tert*-butyl ester form of **10** with K_2CO_3 in methanol at room temperature afforded the Boc-protected azidohomo-phenylalanine derivative **11** with recovery of the directing group, 5-methylisoxazole-3-carboxylate as the methyl ester. On the other hand, the methyl ester form of compound **10** when treated with 1 N aq NaOH in methanol provided the Boc-protected homophenylalanine derivative **12**, which can be directly used for peptide synthesis.

As a demonstration of the usefulness of our method in organic synthesis, compound **8b** was treated with $NaBH_4$ in ethanol to reduce the ethyl ester to alcohol **13** (Scheme 2). The

Scheme 2. Transformation of the Alkylated Thr Derivative to a Key Synthon for (−)-Banalol



terminal alcohol was mesylated and further converted to an azide **14**. Subsequent Boc protection of **14**, followed by removal of MICA directing group with K_2CO_3 in methanol, afforded the fully protected ε-azido-β-hydroxy amino acid derivative **16**, a key intermediate for the total synthesis of the natural product (−)-balanol **17**, a potent PKC inhibitor.[15]

In summary, we have shown that the previously unexplored isoxazole-3-carboxamide and oxazole-4-carboxamide moieties provide new scaffolds for designing bidentate auxiliaries in Pd-catalyzed C−H activation. In particular, 5-methylisoxazole-3-carboxamide (MICA) is highly efficient in directing Pd-catalyzed arylation and alkylation of unactivated γ-C(sp^3)−H bonds. These reactions operate under mild conditions and confer high regio- and stereoselectivity. Using this methodology, we have prepared a diverse array of unnatural amino acids that can be used as building blocks for peptidomimetics and for several important bioactive compounds of therapeutic interest.[16] The high efficiency of MICA as a directing group as well as its easy introduction and removal make it a robust

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auxiliary that may also be useful for other C−H functionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03118.

Experimental procedures and detailed characterization data of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cfliu@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

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