125 Jahre Angewandte Chemie

DOI: 10.1002/ange.201306625

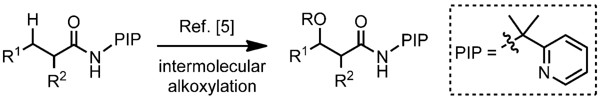
β-Lactam Synthesis

Stereoselective Synthesis of Chiral α-Amino-β-Lactams through Palladium(II)-Catalyzed Sequential Monoarylation/Amidation of C(sp^3)–H Bonds**

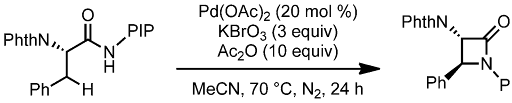
*Qi Zhang, Kai Chen, Weihao Rao, Yuejun Zhang, Fa-Jie Chen, and Bing-Feng Shi**

Since the discovery of penicillin nearly a century ago, β-lactam antibiotics have continued to capture the attention of the synthetic and medicinal chemistry communities. In particular, the α-amino-β-lactam motif is present in both penicillin and cephalosporin. It is also a versatile chiral building block in organic synthesis. Consequently, the preparation of α-amino-β-lactams has been the topic of extensive research efforts, and many stereoselective approaches toward these compounds have been developed. The asymmetric methods used include the Staudinger ketene–imine [2+2] cycloaddition, Kinugasa alkyne–nitrone cycloaddition, and Gilman–Speeter ester enolate–imine condensation.[1]

The seminal work of Daugulis and co-workers on the palladium-catalyzed arylation of secondary C(sp^3)–H bonds with an 8-aminoquinoline-derived N,N-bidentate directing group[2] has inspired several research groups to use this type of auxiliary to develop a diverse collection of novel C(sp^3)–H functionalization reactions.[3] Moreover, this chemistry has been applied in the total synthesis of natural products.[4] Encouraged by these elegant studies, we recently developed a modified bidentate pyridine-containing directing group derived from 2-(pyridin-2-yl)isopropylamine. This directing group exhibited superior reactivity in the activation of methylene C(sp^3)–H bonds. For example, the use of the 2-(pyridin-2-yl)isopropyl (PIP) directing group was instrumental in the development of a palladium-catalyzed methylene C(sp^3)–H alkoxylation [Eq. (1)].[5] During the course of our investigations, we found that when $KBrO_3$ was used as the oxidant, the phenylalanine derivative **2a** was transformed into α-amino-β-lactam **3a** in 16% yield, presumably through intramolecular C(sp^3)–H amidation of the methylene group [Eq. (2) (Phth = phthaloyl)]. On the basis of these results, we postulated that we could develop a stereoselective route to highly functionalized α-amino-β-lactams from simple alanine derivatives by using this methylene C(sp^3)–H amidation reaction as the second step of a two-step C(sp^3)–H monoarylation/amidation sequence (Scheme 1).



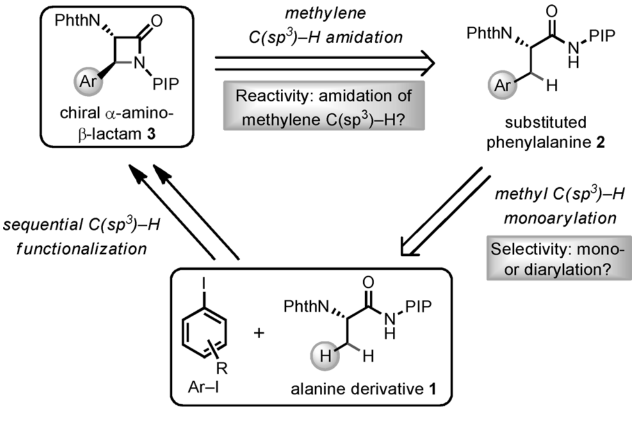
(1)



2a **3a**, 16%

(2)

At the outset, two evident challenges warranted consideration (Scheme 1). First, in the initial C(sp^3)–H arylation step, the selectivity for mono- versus diarylation would need to be controlled in such a way that a general method for selective methyl C(sp^3)–H monoarylation of the alanine derivatives **1** could be developed. Daugulis and co-workers previously reported that the use of a 2-thiomethylaniline-based auxiliary facilitated the selective monoarylation of methyl groups.[2b,c] The thioether functionality in this directing group, however, is labile and susceptible to oxidation under the conditions that would be required in the subsequent C(sp^3)–H amidation step. Yu and co-workers reported the selective monoarylation of methyl groups with a weakly coordinating *N*-aryl amide auxiliary.[6a] This directing group,



Scheme 1. Stereoselective synthesis of α-amino-β-lactams through palladium-catalyzed sequential C(sp^3)–H functionalization.

---

[*] Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, Prof. Dr. B.-F. Shi
Department of Chemistry, Zhejiang University
Hangzhou 310027 (China)
E-mail: bfshi@zju.edu.cn
Homepage: http://mypage.zju.edu.cn/bfshi
Prof. Dr. B.-F. Shi
State Key Laboratory of Bioorganic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
Shanghai 200032 (China)

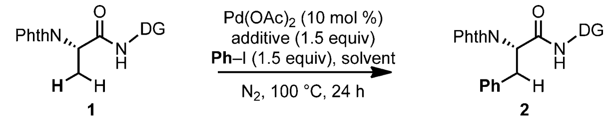
[**] We are grateful to Dr. Keary M. Engle (California Institute of Technology) for helpful suggestions and comments on this manuscript. Financial support from the NSFC (21002087, 21272206, J1210042), the Fundamental Research Funds for the Central Universities (2010QNA3033), Zhejiang Provincial NSFC (Z12B02000), the Qianjiang Project (2013R10033), and the Ministry of Education (SRFDP 20110101110005) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306625.

however, has not been used successfully with starting materials derived from α-amino acids and has not been applied in C(sp^3)–H amination.[6b,c] In contrast, although the 8-aminoquinoline-based auxiliary described by Daugulis and co-workers is stable under various oxidative conditions and has been successfully used in α-amino acid functionalization, only moderate monoselectivity was observed.[7] Thus, an alternative directing group with high reactivity in C(sp^3)–H arylation and selectivity for monoarylation is needed.

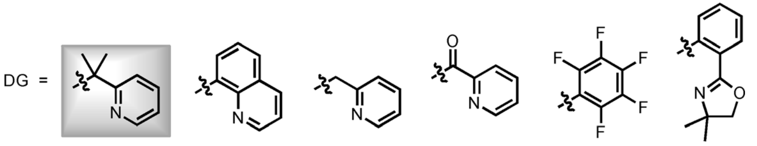
Second, sufficiently high reactivity would be required to activate the newly formed benzylic methylene C(sp^3)–H bond in the subsequent amidation step.[8] Transition-metal-catalyzed C–H activation/C–N bond formation has emerged as a powerful method for the construction of N heterocycles.[9] Among the transition metals, palladium has proven to be especially versatile in this respect.[10–14] A number of synthetic protocols based on palladium-catalyzed C(sp^2)–H amination have been developed for the synthesis of carbazoles, indazoles, indoles, indolines, and related compounds.[10] In contrast, the development of analogous routes to saturated N heterocycles on the basis of C(sp^3)–H amination has remained a challenge.[11–13] Recently, the research groups of Daugulis and Chen independently developed elegant methods for the palladium-catalyzed intramolecular amination of primary C(sp^3)–H bonds to form azetidines, pyrrolidines, and indolines.[12] Subsequently, Shi and co-workers reported an example of the intramolecular amination of primary C(sp^3)–H bonds with a triazole acid auxiliary as a directing group.[13] We envisioned that methodology for the synthesis of N heterocycles through the amination of *secondary* C(sp^3)–H bonds would be a valuable addition to the heterocyclic chemistry toolkit and offer a new retrosynthetic disconnection for access to commonly encountered structural motifs.[15]

Table 1: Optimization of the reaction conditions for methyl C(sp^3)–H monoarylation.[a]



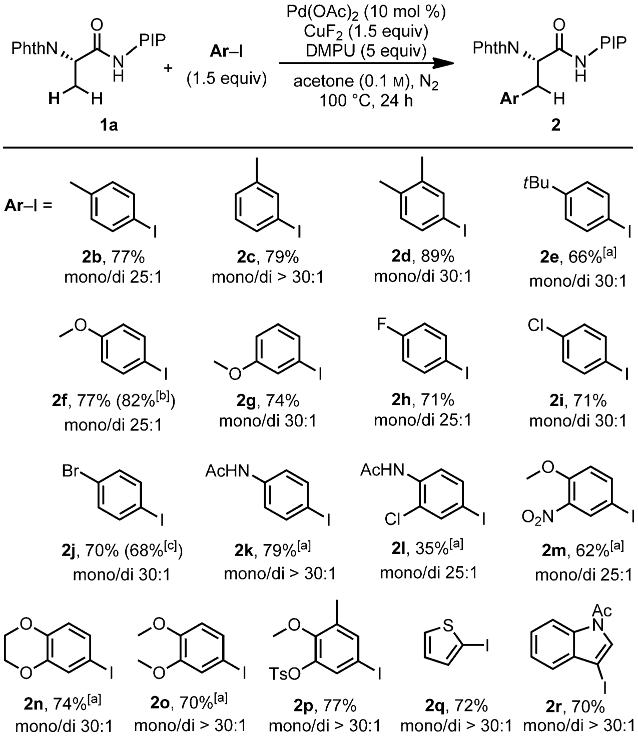
Entry	Substrate	Additive	Solvent	Yield [%][b]	Ratio (mono/di)[c]
1[d]	**1a**	AgOAc	neat	87	2:7
2[e]	**1a**	AgOAc	*t*BuOH	52	1:4
3[f]	**1a**	K_2CO_3	2-methyl-2-butanol/H_2O (4:1)	–	–
4	**1a**	Cu(OAc)$_2$	PhCl	43	3:1
5	**1a**	$CuCl_2$	PhCl	trace	–
6	**1a**	CuOAc	PhCl	35	2.2:1
7	**1a**	CuCl	PhCl	22	> 20:1
8	**1a**	CuF_2	PhCl	44	11:1
9	**1a**	CuF_2	acetone	60	20:1
10	**1a**	CuF_2	DMA	69	30:1
11	**1a**	CuF_2	MeCN	trace	–
12	**1a**	CuF_2	DMPU	75	17:1
13[g]	**1a**	**CuF_2**	**acetone/DMPU (5 equiv)**	**81 (99% *ee*)**	**25:1**
14[g,h]	**1a**	CuF_2	acetone/DMPU (5 equiv)	0	–
15[g]	**1b**	CuF_2	acetone/DMPU (5 equiv)	77	4.3:1
16[g]	**1c**	CuF_2	acetone/DMPU (5 equiv)	16	mono
17[f,g]	**1d**	CuF_2	acetone/DMPU (5 equiv)	–	–
18[g]	**1e**	CuF_2	acetone/DMPU (5 equiv)	NR	–
19[g]	**1f**	CuF_2	acetone/DMPU (5 equiv)	NR	–

[a] Reaction conditions: **1** (0.1 mmol), Pd(OAc)$_2$ (0.01 mmol), additive (0.15 mmol), PhI (0.15 mmol), solvent (0.1 M), 100 °C, N_2 atmosphere. [b] Yield of the isolated product. [c] The ratio of the mono- to the diarylated product was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The reaction was carried out with 18 equivalents of PhI. [e] The reaction was carried out with 4.0 equivalents of PhI. [f] Decomposition of the starting material was observed. [g] The reaction was carried out on a 0.2 mmol scale. [h] Bromobenzene was used as the coupling partner. DMA = dimethylacetamide, DMPU = *N*,*N'*-dimethylpropyleneurea, NR = no reaction.



1a **1b** **1c** **1d** **1e** **1f**

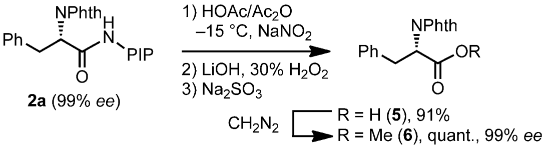
We envisioned that our new PIP directing group would meet these challenges through careful tuning of the reaction conditions. It is well-established that the combination of aryl iodides and silver(I) salts has broad application in palladium-catalyzed arylation.[2,3a,16] We commenced our studies by applying reaction conditions previously established by Daugulis and co-workers. However, poor selectivity was observed when PhI or *t*BuOH was used as the solvent (Table 1, entries 1 and 2). When the reaction was conducted in a 2-methyl-2-butanol/water mixture in the presence of K_2CO_3,[2b] decomposition of **1a** was observed, presumably owing to the hydrolysis of the *N*-phthaloyl protecting group under aqueous basic conditions (Table 1, entry 3). We screened copper salts as iodide scavengers and were delighted to find that the use of CuF_2 improved both the yield and selectivity of the reaction (44% yield, mono/di 11:1; Table 1, entry 8). Further screening revealed that the use of acetone as the solvent led to further improvements in yield and selectivity (60% yield, mono/di 20:1; Table 1, entry 9). Previously, Tremont and Rahman found that the use of coordinating solvents, such as DMF, DMA, and acetonitrile, promoted exclusive monomethylation in the palladium-catalyzed *ortho* methylation of acetanilides with MeI.[17] Shabashov and Daugulis also found that reactions run in acetonitrile cleanly afforded the monoarylation product.[2b] In the present reaction, the use of coordinating solvents, such as DMA and DMPU, did improve the selectivity (Table 1, entries 10 and 12), presumably through the same inhibitory effect described by Tremont and Rahman.[17] After further optimization, we were pleased to find that the monoarylation of **1** with PhI (1.5 equiv) occurred in 81 % yield with high selectivity (mono/di 25:1) in the presence of $Pd(OAc)_2$ (10 mol %), CuF_2 (1.5 equiv), and DMPU (5 equiv) when the reaction was carried out in acetone (0.1 M) under N_2 at 100 °C for 24 h (Table 1, entry 13). Notably, the monoarylated product **2a** was obtained without any observable epimerization (99 % *ee*; see the Supporting Information for details). No coupling occurred with bromobenzene as the coupling partner (Table 1, entry 14).



Scheme 2. Scope of the methyl $C(sp^3)$–H monoarylation. Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), CuF_2 (0.3 mmol), ArI (0.3 mmol), DMPU (1 mmol), acetone (2 mL), N_2 atmosphere, 100 °C, 24 h. Yields given are for the isolated product. The ratio of the mono- to the diarylated product was determined by ^1H NMR spectroscopy of the crude reaction mixture. [a] The reaction was carried out with 1 equivalent of DMPU. [b] The reaction was carried out on a 1 mmol scale. [c] The reaction was carried out on a 5 mmol scale.

We carried out control reactions with alternative directing groups under the optimized conditions (Table 1, entries 15–19). 8-Aminoquinoline (substrate **1b**) gave a satisfactory yield and moderate selectivity (77 % yield, mono/di 4.3:1; Table 1, entry 15), whereas the use of 2-aminomethylpyridine as the directing group (substrate **1c**) led exclusively to the monoarylated product in only 16 % yield with significant decomposition of the starting material (Table 1, entry 16).[18] The picolinic imide **1d** decomposed under the current reaction conditions (Table 1, entry 17). No reaction occurred when the weakly coordinating *N*-aryl amide **1e** or substrate **1f** with a bidentate auxiliary was used (Table 1, entries 18 and 19).

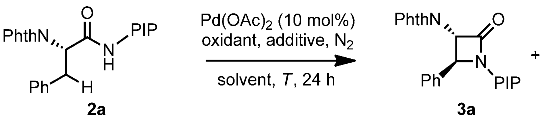
A wide range of aryl iodides were found to be compatible with this protocol, and the desired products were furnished in good yields under the optimized reaction conditions (Scheme 2). Many different functional groups, such as alkoxy (products **2f** and **2g**, 77 and 74 %, respectively), fluoro (product **2h**, 71 %), chloro (product **2i**, 71 %), bromo (product **2j**, 70 %), nitro (product **2m**, 62 %), and acetylamino groups (products **2k** and **2l**, 79 and 35 %, respectively), were tolerated under the reaction conditions. Moreover, di- and trisubstituted aryl iodides were also coupled under the standard conditions to afford the desired products in moderate to good yields (products **2d**, **2l–p**). The reaction also proceeded well with heterocyclic coupling partners, including 2-iodothiophene (product **2q**, 72 %) and 3-iodoindole (product **2r**, 70 %). Excellent selectivity for monoarylation was observed under our optimized conditions (mono/di ≥ 25:1). When the reaction was attempted on a larger scale, the yields were essentially the same (product **2f**, 1 mmol scale: 82 % yield; product **2j**, 5 mmol scale: 68 % yield). After the reaction, the directing group can also be removed in high yield through a mild N-nitrosylation/hydrolysis sequence. Following esterification, the corresponding methyl ester **6** was obtained in quantitative yield with 99 % *ee* [Eq. (3); see the Supporting Information for details]. Thus, our monoarylation procedure provides an efficient strategy for the synthesis of substituted phenylalanine derivatives.



(3)

Subsequently, we turned our attention to the second step, intramolecular methylene $C(sp^3)$–H amidation of phenylalanine derivative **2a** (Table 2). $PhI(OAc)_2$ was

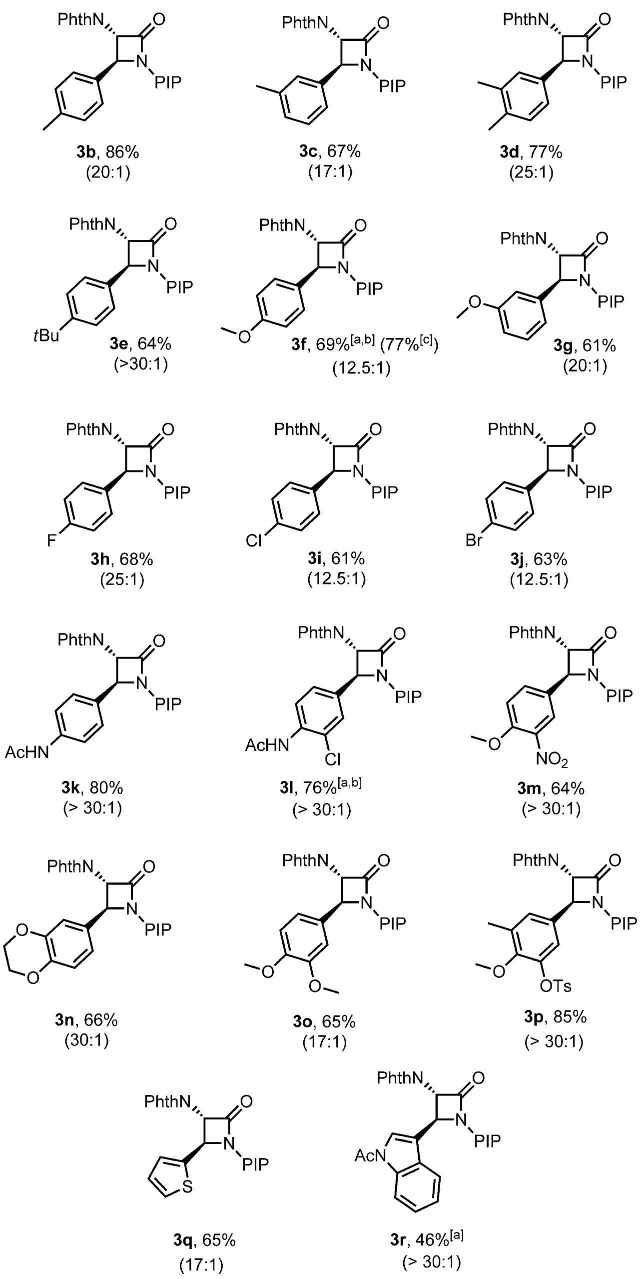
Table 2: Optimization of the reaction conditions for methylene $C(sp^3)$–H amidation.



Entry	Oxidant (equiv)	Additive (equiv)	*T* [°C]	Solvent	Yield [%][a]	**3a/4a**[b]
1[c]	$PhI(OAc)_2$ (2.5)	AcOH (2)	110	toluene	56	**4a** (d.r. 1.9:1)
2[c]	$PhI(OAc)_2$ (2.5)	none	90	toluene	78	**4a** (d.r. 2.1:1)
3	$NaIO_4$ (3)	Ac_2O (5)	70	MeCN	53	6.5:1
4	$NaIO_4$ (3)	none	70	MeCN	0	–
5	$NaIO_4$ (3)	Ac_2O (10)	70	MeCN	77	6.7:1
6	$NaIO_4$ (3)	Ac_2O (10)	70	EtOAc	42	1.4:1
7	$NaIO_4$ (3)	Ac_2O (10)	70	1,4-dioxane	50	5:1
8	$NaIO_4$ (3)	Ac_2O (10)	70	DMF	18	4:1
9	$NaIO_4$ (3)	Ac_2O (10)	70	acetone	< 5	–
10	$NaIO_3$ (3)	Ac_2O (10)	70	MeCN	74	12.5:1

[a] Yield of the isolated product (unless otherwise specified). [b] The ratio of **3a** to **4a** was determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] The yield and diastereomeric ratio of the acetoxylated product **4a** were determined by ^1H NMR spectroscopy of the crude reaction mixture. DMF = *N*,*N*-dimethylformamide.

first tested as the oxidant.[19] However, the use of PhI(OAc)$_2$ predominantly led to the acetoxylated product **4a** and a significant amount of decomposition, and none of the desired product was obtained (Table 2, entries 1 and 2). Sodium periodate has previously been used as a stoichiometric oxidant for the oxidation of low-valent ruthenium to ruthenium tetraoxide.[20a,b] It is compatible with a wide range of functional groups and is sparingly soluble in most organic solvents.[20c] We reasoned that the combination of NaIO$_4$ with Ac$_2$O might lead to the slow release of IO$_{4-n}$(OAc)$_{2n-1}$, which should be soluble in MeCN and could oxidize the key cyclopalladated Pd^{II} intermediate to Pd^{IV} to promote C–N reductive elimination.[21] We were pleased to find that the use of NaIO$_4$ (3 equiv) and Ac$_2$O (5 equiv) gave the lactam product **3a** in 53 % yield (Table 2, entry 3). No product was observed in the absence of Ac$_2$O (Table 2, entry 4), and the use of 10 equivalents of Ac$_2$O was ultimately found to give the highest yield (77 %; Table 2, entry 5). These experiments confirmed that Ac$_2$O is critical for the amidation reaction. The use of other solvents resulted in lower yields (Table 2, entries 6–9). Through subsequent optimization, we identified NaIO$_3$ as the best overall oxidant in terms of reactivity and chemoselectivity (74 % yield, **3a**/**4a** 12.5:1; Table 2, entry 10).



Scheme 3. Scope of the intramolecular methylene C(sp^3)–H amidation to form α-amino-β-lactams **3**. Reaction conditions: **2** (0.15 mmol), Pd(OAc)$_2$ (10 mol%), NaIO$_3$ (0.3 mmol), Ac$_2$O (1.5 mmol), MeCN (3 mL), N$_2$ atmosphere, 70 °C, 48 h. Yields given are for the isolated product. The ratio of the β-lactam to the β-acetoxylation product was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [a] The reaction was carried out with 3 equivalents of NaIO$_3$. [b] Reaction time: 24 h. [c] The reaction was carried out on a 0.84 mmol scale with 3 equivalents of NaIO$_4$.

Having developed this robust protocol for intramolecular benzylic C(sp^3)–H amidation, we attempted a sequential C(sp^3)–H monoarylation/amidation. Gratifyingly, we found that all monoarylated products **2** in Scheme 2 could be used as substrates for intramolecular benzylic C(sp^3)–H amidation (Scheme 3).[22] Generally, under the standard conditions, only a single diastereoisomer was observed, along with a small quantity of the corresponding β-acetoxylated by-product. The configuration of **3f** was confirmed unambiguously by X-ray diffraction, and all other lactam products **3** were assigned by analogy on the basis of similarities in their ^{1}H NMR spectra (see the Supporting Information).[23] The *trans* orientation of the *N*-Phth group and the phenyl ring was consistent with the proposed stereochemical model, according to which the formation of the *trans* palladacycle intermediate is favored on steric grounds (see the Supporting Information).[2c,3a,24] Next, oxidation and stereoretentive C–N reductive elimination takes place to release the product and close the catalytic cycle.

In conclusion, we have developed a stereoselective synthesis of α-amino-β-lactams from starting materials that can be conveniently prepared from alanine through palladium(II)-catalyzed sequential C(sp^3)–H monoarylation/amidation. The N,N-bidentate PIP amide directing group was found to be effective both in controlling selectivity in the arylation step for monoarylation and in enhancing reactivity in the amination step. This process is functional-group-tolerant, and the resulting α-amino-β-lactam products were obtained in moderate to high yields. This procedure demonstrates the power of sequential C–H functionalization to streamline the synthesis of complex, enantiomerically pure heterocycles from readily available starting materials. Further studies toward the application of this reaction to the synthesis of complex targets and the elucidation of the mechanistic details of the process are under way.

Received: July 29, 2013
Revised: September 28, 2013

Keywords: amidation · arylation · C–H activation · β-lactams · palladium

---

[1] For selected reviews and leading references on asymmetric approaches, see: a) S. France, A. Weatherwax, A. E. Taggi, T. Lectka, *Acc. Chem. Res.* **2004**, *37*, 592; b) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Curr. Med. Chem.* **2004**, *11*, 1837; c) M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 4572; d) R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082; e) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578; f) J. Marco-Contelles, *Angew. Chem.* **2004**, *116*, 2248; *Angew. Chem. Int. Ed.* **2004**, *43*, 2198.

[2] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965; c) L. D. Tran, O. Daugulis, *Angew. Chem.* **2012**, *124*, 5278; *Angew. Chem. Int. Ed.* **2012**, *51*, 5188.

[3] a) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391; b) Y. Feng, Y. Wang, B. Landgraf, S. Liu, G. Chen, *Org. Lett.* **2010**, *12*, 3414; c) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984; d) R. Shang, L. Ilies, A. Matsumoto, E. Nakamura, *J. Am. Chem. Soc.* **2013**, *135*, 6030.

[4] a) W. R. Gutekunst, R. Gianatassio, P. S. Baran, *Angew. Chem.* **2012**, *124*, 7625; *Angew. Chem. Int. Ed.* **2012**, *51*, 7507; b) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076; c) Y. Feng, G. Chen, *Angew. Chem.* **2010**, *122*, 970; *Angew. Chem. Int. Ed.* **2010**, *49*, 958.

[5] F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang, B.-F. Shi, *Chem. Sci.* **2013**, *4*, 4187.

[6] a) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886; b) M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598; c) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 18570.

[7] Daugulis and co-workers[2c] and Corey and co-workers[3a] have reported the diarylation of **1b**. Shabashov and Daugulis also reported the arylation of *N*-(quinolin-8-yl)propionamide with moderate selectivity for monoarylation (mono-/diarylation 3.9:1) without further optimization.[2b]

[8] For selected recent examples of palladium-catalyzed benzylic C–H functionalization, see: a) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 9902; b) P. Xie, C. Xia, H. Huang, *Org. Lett.* **2013**, *15*, 3370.

[9] For selected reviews, see: a) T.-S. Mei, L. Kou, S. Ma, K. M. Engle, J.-Q. Yu, *Synthesis* **2012**, 1778; b) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; c) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874.

[10] For selected examples of the palladium-catalyzed intramolecular amination of $C(sp^2)$–H bonds, see: a) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560; b) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058; c) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 16184; d) T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806; e) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; f) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312; g) G. He, C. Lu, Y. Zhao, W. A. Nack, G. Chen, *Org. Lett.* **2012**, *14*, 2944; h) T.-S. Mei, D. Leow, H. Xiao, B. N. Laforteza, J.-Q. Yu, *Org. Lett.* **2013**, *15*, 3058.

[11] J. J. Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem.* **2009**, *121*, 7024; *Angew. Chem. Int. Ed.* **2009**, *48*, 6892.

[12] a) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; b) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7. During the revision of this manuscript, an intramolecular amination of primary $C(sp^3)$–H bonds was described: c) G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem.* **2013**, *125*, 11330; *Angew. Chem. Int. Ed.* **2013**, *52*, 11124.

[13] X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen, X. Shi, *Chem. Sci.* **2013**, *4*, 3712.

[14] For examples of the palladium-catalyzed intermolecular amination of C–H bonds, see: a) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048; b) K.-H. Ng, A. S. C. Chan, W.-Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862; c) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 8806; *Angew. Chem. Int. Ed.* **2011**, *50*, 8647; d) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1466; e) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1694; f) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652; g) Á. Iglesias, R. Álvarez, Á. R. de Lera, K. Muñiz, *Angew. Chem.* **2012**, *124*, 2268; *Angew. Chem. Int. Ed.* **2012**, *51*, 2225; h) R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 8480.

[15] For recent reviews on C–H functionalization in organic synthesis, see: a) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976; b) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; d) L. Yang, H. Huang, *Catal. Sci. Technol.* **2012**, *2*, 1099.

[16] For selected leading references on the palladium-catalyzed arylation of C–H bonds by the use of a combination of aryl iodides and silver salts, see: a) O. Daugulis, V. G. Zaitsev, *Angew. Chem.* **2005**, *117*, 4114; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; b) D. Shabashov, O. Daugulis, *Org. Lett.* **2005**, *7*, 3657; c) D. Shabashov, O. Daugulis, *Org. Lett.* **2006**, *8*, 4947; d) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879, and references therein.

[17] S. J. Tremont, H. U. Rahman, *J. Am. Chem. Soc.* **1984**, *106*, 5759.

[18] The 2-aminomethylpyridine auxiliary was susceptible to decomposition under the reaction conditions; see Ref. [2a].

[19] For applications of $PhI(OAc)_2$ in C–H oxidation, see: a) T. Yoneyama, R. H. Crabtree, *J. Mol. Catal. A: Chem.* **1996**, *108*, 35; b) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300.

[20] a) C. Djerassi, R. R. Engle, *J. Am. Chem. Soc.* **1953**, *75*, 3838; b) P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936; c) T. K. M. Shing in *Comprehensive Organic Synthesis*, *Vol. 7* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 703–716.

[21] A plausible rationale for the generation of an active $IO_{4-n}(OAc)_{2n-1}$ species is hypothesized in analogy to the formation of Dess–Martin periodinane from IBX.

[22] We tested a range of plausible conditions for cleavage of the PIP group following cyclization without success. We are currently investigating alternative possibilities and will report our findings in due course.

[23] CCDC 949097 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] We recently synthesized and characterized a related *trans* palladacycle: K. Chen, F. Hu, S.-Q. Zhang, B.-F. Shi, *Chem. Sci.* **2013**, *4*, 3906.