A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Palladium-Catalyzed Construction of Quaternary Stereocenters by Enantioselective Arylation of γ-Lactams with Aryl Chlorides and Bromides

Authors: Carina Jette, Irina Geibel, Shoshana Bachman, Masaki Hayashi, Shunya Sakurai, Hideki Shimizu, Jeremy B. Morgan, and Brian Stoltz

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201814475
Angew. Chem. 10.1002/ange.201814475

Link to VoR: http://dx.doi.org/10.1002/anie.201814475
http://dx.doi.org/10.1002/ange.201814475

WILEY-VCH

10.1002/anie.201814475

WILEY-VCH

Palladium-Catalyzed Construction of Quaternary Stereocenters by Enantioselective Arylation of γ-Lactams with Aryl Chlorides and Bromides

Carina I. Jette[a], Irina Geibel[a], Shoshana Bachman[a], Masaki Hayashi[a], Shunya Sakurai[a], Hideki Shimizu[a], Jeremy B. Morgan* [b], Brian M. Stoltz* [a]

Abstract: Herein, we report the first Pd-catalyzed enantioselective arylation of α-substituted γ-lactams. Two sets of conditions were developed for this transformation, allowing for the use of either aryl chlorides or bromides as electrophiles. Utilizing a highly electron-rich, dialkylphosphine ligand, we have been able to construct α-quaternary centers in good yields (up to 91% yield) and high enantioselectivities (up to 97% ee).

Nitrogen heterocycles are ubiquitous structural motifs that can be found across all areas and applications of organic chemistry. A particularly important subgroup of this class are the pyrrolidinones, which along with their saturated counterparts the pyrrolidines, occur widely in nature,[1,2] possess a wide range of biological and pharmacological properties,[3] and are employed in materials[4] and catalysis.[5] For these reasons, the development of stereoselective approaches to functionalized five-membered nitrogen-containing heterocycles is a topic of great interest in the synthesis of small molecules and natural products.

Our group has a long-standing interest in the stereoselective synthesis of five-membered N-heterocyclic building blocks, having developed methods for both enantioselective allylic alkylation[6] and enantioselective α-acylation of γ-butyrolactams.[7] The α-aryl pyrrolidinone building block is of special interest, as it would enable access to the phenethylbenzylamine structural motif, which is prevalent in a number of biologically active natural products and drug-like molecules (Figure 1a).[8] Nevertheless, methods describing the asymmetric α-arylation of substituted pyrrolidinones to produce α-quaternary lactams have previously remained elusive.

Despite the apparent similarities to other known α-arylation reactions, there are a number of subtle challenges that have potentially precluded α-substituted γ-lactams from having been successfully implemented in Pd-catayzed asymmetric α-arylation chemistry. One of the challenges associated with the use of lactams in metal-catalyzed enolate arylation is the necessity for enolization by strong base, which may lead to the generation of unwanted aryne intermediates from the aryl halide[9,10] in addition to catalyst decomposition. As a result, prior reports are limited to either α-unsubstituted piperidinones, which require pre-formation of a basicity-tempered zinc enolate to generate the desired product, or oxindoles,[11] a special case that does not require high temperatures or strongly basic conditions (Figure 1b).[12] A crucial step in the development of this transformation would be the identification of a catalyst that not only possesses optimal steric and electronic properties, but also exhibits good stability under basic conditions. Taking these considerations into account, we sought to develop the first method for the direct transition metal-catalyzed enantioselective α-arylation of α-substituted γ-lactams to generate all-carbon quaternary stereocenters.

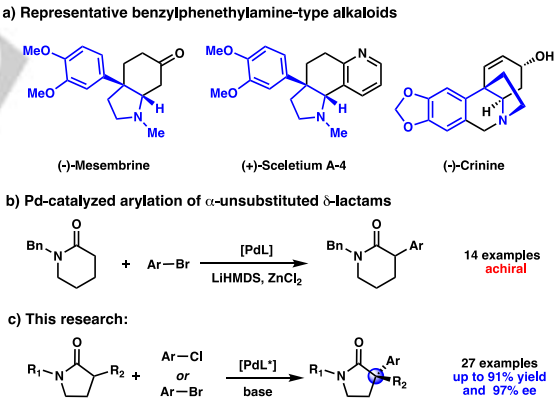


Figure 1. Representative benzylphenethylamine-type alkaloids and state of the art in transition metal-catalyzed α-arylation of monocyclic lactams.

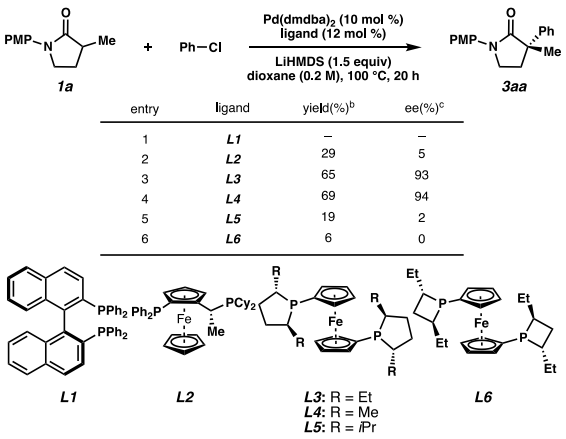
We initiated our investigation into the enantioselective α-arylation of *N*-*p*-methoxyphenyl (PMP) α-methyl pyrrolidinone (**1a**) with chlorobenzene by examining the effect of a number of different ligands on the reactivity and selectivity of the reaction (Table 1).[13] With $Pd(dmdba)_2$ as the Pd source, commonly employed ligands (*S*)-BINAP (entry 1) and Josiphos (entry 2) resulted in both low yields and low enantiomeric excess. We found that the ferrocelane class of ligands (**L3**-**L5**) was optimal; both **L3** (entry 3) and **L4** (entry 4) resulted in the formation of the desired α-quaternary lactam **3aa** in equally high yield and high enantiomeric excess. However, the use of the bulkier **L5** led to

[a] Carina I. Jette, Irina Geibel, Shoshana Bachman, Masaki Hayashi, Hideki Shimizu, Brian M. Stoltz
Warren And Katharine Schlinger Laboratory for Chemistry and Chemical Engineering
Division of Chemistry and Chemical Engineering
California Institute of Technology
1200 E. California Blvd. MC 101-20, Pasadena CA 91125 (USA)
E-mail: stoltz@caltech.edu
[b] Jeremy B. Morgan
Dobo Hall
Department of Chemistry and Biochemistry,
University of North Carolina Wilmington, NC 28403 (USA)

Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201814475

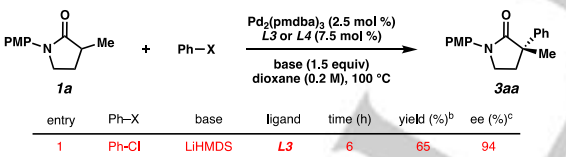
both diminished yield and enantioselectivity. Crucially, these highly electron-rich dialkylphosphine ligands should undergo rapid oxidative addition to the aryl halide, while the large bite angle should encourage facile reductive elimination.[14] Furthermore, since alkyl phosphines are less susceptible to P–C cleavage[15], we believe that these ligands might form a Pd/ligand complex that is more stable at high temperatures. Interestingly, we noted that the structurally similar phosphonato FerroTANE ligand (**L6**) (entry 6) resulted in low conversion.



entry	ligand	yield(%)[b]	ee(%)[c]
1	*L1*	–	–
2	*L2*	29	5
3	*L3*	65	93
4	*L4*	69	94
5	*L5*	19	2
6	*L6*	6	0

Table 1. Evaluation of Ligands for Pd-Catalyzed α-Arylation of γ-Lactams.[a]

[a] Conditions: 0.1 mmol scale, **1a** (1.5 equiv), **2a** (1.0 equiv), LiHMDS (1.5 equiv), 10 mol % $Pd(dmdba)_2$, 12 mol % ligand, 0.5 mL dioxane. [b] Determined by LC-MS analysis of the crude reaction mixture using 1,3,5–trimethoxybenzene as a standard. [c] Determined by chiral SFC analysis of the isolated product. PMP = *p*-methoxyphenyl. dmdba = 3,5,3',5'–dimethoxydibenzylideneacetone .



entry	Ph–X	base	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	Ph-Cl	LiHMDS	*L3*	6	65	94
2	Ph-I	LiHMDS	*L3*	20	–	–
3	Ph-OTf	LiHMDS	*L3*	20	–	–
4	Ph-Cl	NaHMDS	*L3*	20	39	55
5	Ph-Cl	KHMDS	*L3*	20	7	–
6[d]	Ph-Br	NaHMDS	*L3*	16	64	96
7	Ph-Br	NaHMDS	*L4*	12	86	92
8	Ph-Br	LiHMDS	*L4*	15	31	72
9[d]	Ph-Br	NaHMDS	*L4*	15	84	92
10[e]	Ph-Br	NaHMDS	*L4*	15	72	92

Table 2. Optimization of Reaction Conditions.[a]

[a] Conditions: 0.1 mmol scale, **1a** (1.5 equiv), Ph–X (1.0 equiv), base 1.5 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), ligand (7.5 mol %), 0.5 mL dioxane. [b] yield determined by LCMS analysis of the crude reaction mixture using 1,3,5–trimethoxybenzene as a standard. [c] Determined by chiral SFC analysis of the isolated product. [d] Reaction performed at 80 °C. [e] Reaction performed at 54 °C. PMP = *p*-methoxyphenyl. pmdba = 4,4' –dimethoxydibenzylideneacetone.

By changing the Pd source, we were able to produce a more active pre-catalyst that allowed for a lower catalyst loading and shorter reaction time with **L3** (Table 2, entry 1). We found that the identity of the base was critical for high yields and enantioselectivities and dependent on the choice of electrophilic coupling partner: when chlorobenzene is used, LiHMDS resulted in the highest yield and enantioselectivity (entries 1, 4, and 5), whereas with bromobenzene, NaHMDS proved optimal (entries 7 and 8). By employing the less hindered ligand **L4,** we were able to isolate **3aa** in 86% yield and 92% ee after 12 hours (entry 7).[16] With this new set of conditions, the reaction proceeds at a lower temperature; the desired product is obtained in 83% yield and 92% ee (entry 8) after 15 h at 80 °C. Moreover, at 54 °C the product is still obtained in good yield and high enantiomeric excess (entry 10).

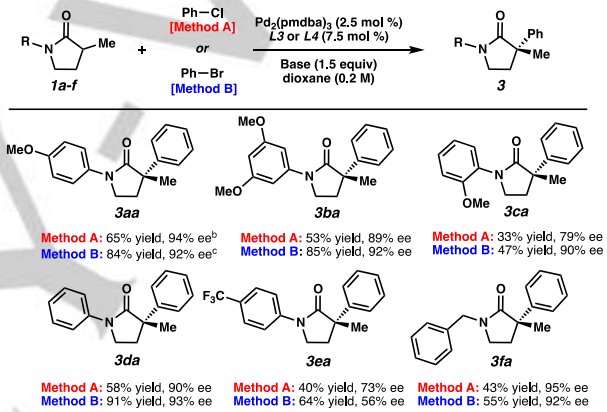


Table 3. Scope of the *N*-Protecting Group.[a]

[a] Conditions for each method are as follows: Method A: lactam (1.5 equiv), Ph–Cl (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol%), **L3** (7.5 mol %), LiHMDS (1.5 equiv), dioxane (0.2 M), 100 °C, 20h. Method B: lactam (1.5 equiv), Ph–Br (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol%), **L4** (7.5 mol%), NaHMDS (1.5 equiv), dioxane (0.2 M), 80 °C, 20 h. [b] 6 h. [c] 15 h. pmdba= 4,4'–dimethoxydibenzylideneacetone.

With optimized conditions for aryl chlorides (Method A, Table 2, entry 1) and aryl bromides (Method B, Table 2, entry 9) in hand, the effect of the *N*-protecting group on the reaction was examined (Table 3). We were pleased to find that a number of different *N*-protecting groups were tolerated in our reaction. Bis-methoxyphenyl lactam **1b** performs just as well as **1a** with Method B, but a slight decrease in yield and enantioselectivity is observed when subjected to Method A (**3ba**). Switching to *ortho*-methoxy phenyl substituted **1c** or electron-deficient trifluoromethylphenyl **1e** led to diminished yield and enantioselectivity (**3ca** and **3ea**). Although *N*-phenyl **1d** does not outperform **1a** in Method A, it does exhibit higher reactivity and enantioselectivity when exposed to Method B, furnishing the desired product in 91% yield and 93% ee (**3da**). Benzyl-protected lactam **1f** affords α-quaternary lactam **3fa** in high levels of enantiomeric excess across both Methods.

Next, we examined the substrate scope of the enantioselective α-arylation (Table 4). We found that aryl bromides and aryl chlorides with a variety of substitution patterns are accommodated in the arylation. Aryl halides possessing electron-deficient (see products **3ab**, **3ad**, **3ah**,[17] **3ae**) and electron-rich (**3af**, **3ag**) substituents at the *para* position led to products with excellent enantioselectivites using Method A and B respectively. Aryl halides possessing substituents at the *meta* position are also permissible in both Method A and B, although slightly diminished enantioselectivity is observed when 3-chloroanisole is used as the electrophile (**3ai**). Unfortunately, only trace product is observed when *ortho*-substituted aryl halides are exposed to our reaction conditions.[18] Gratifiyingly, an *N*-methyl indole was also tolerated, as we obtained 5-indolyl lactam **3al** in moderate yield and excellent enantioselectivity.

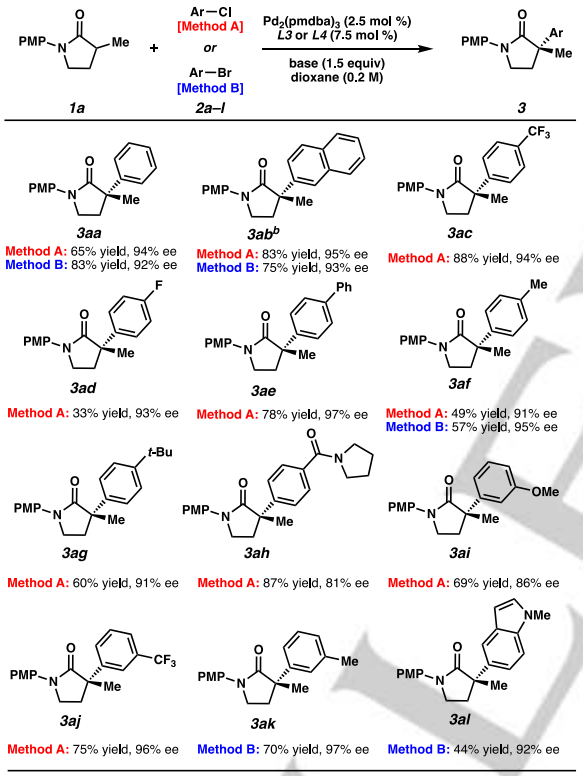


Table 4. Scope of the Aryl Halide.[a]

[a] Conditions for each method are as follows: Method A: **1a** (1.5 equiv), Ar–Cl (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), **L3** (7.5 mol %), LiHMDS (1.5 equiv), dioxane (0.2 M), 100 °C, 6 h. Method B: lactam (1.5 equiv), Ar–Br (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), **L4** (7.5 mol %) NaHMDS (1.5 equiv), dioxane (0.2 M), 80 °C, 15 h. [b] Absolute configuration determined *via* single crystal X-ray analysis. PMP = *p*-methoxyphenyl. pmdba = 4,4' –dimethoxydibenzylideneacetone.

The scope of substitution at the lactam α-carbon was then examined (Table 5). We found that sterically demanding α-substituents are well tolerated in both Methods. Although the yields are slightly diminished, the high levels of enantioselectivity are retained. Examples having ethyl (**3ha**, **3hb**), benzyl (**3ga**, **3gb**), propyl (**3ia)**, phenethyl (**3ja**), and 2-naphthylmethyl (**3ka**) substitution all furnish the α-arylated products in good enantioselectivity. α-Benzyl substituted lactam **1g** was also employed in the reaction with a number of different electrophilic coupling partners using both Methods. Even with a more hindered substrate, similar patterns of reactivity and selectivity to α-methyl substituted **1a** were observed. When an electron-deficient aryl chloride coupling partner is used in Method A or *m*-bromotoluene is used in Method B with **1g**, the desired product is formed in high enantioselectivity and good yield (**3gc** and **3gd**).

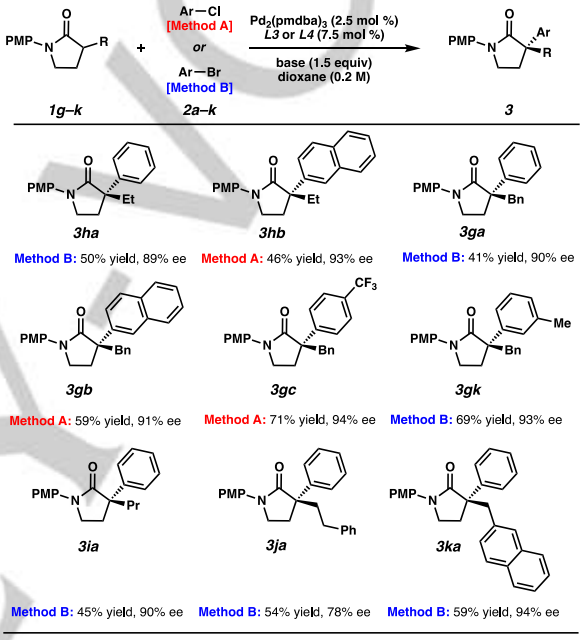
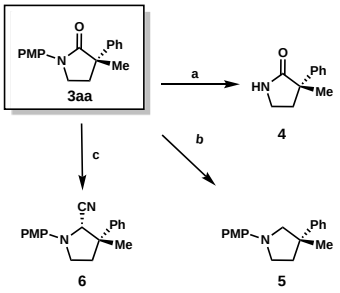


Table 5. Scope of the Lactam.[a]

[a] Conditions for each method are as follows: Method A: lactam (1.5 equiv), Ar–Cl (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), **L3** (7.5 mol %) LiHMDS (1.5 equiv), dioxane (0.2 M), 100 °C, 20 h. Method B: lactam (1.5 equiv), Ar–Br (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), **L4** (7.5 mol %) NaHMDS (1.5 equiv), dioxane (0.2 M), 80 °C, 20 h. PMP = *p*-methoxyphenyl. pmdba = 4,4' –dimethoxydibenzylideneacetone.

Recognizing the potential value of these enantioenriched, quaternary center-containing heterocycles to the synthetic and pharmaceutical communities, we sought to utilize this new transformation in the preparation of differentially substitutes five-membered heterocycles (Scheme 1). α-Quaternary lactam **3aa** can be swiftly deprotected with ceric ammonium nitrate (CAN) providing unprotected lactam **4** in 73% yield. Reduction of the lactam carbonyl with lithium aluminum hydride provides the corresponding medicinally valuable pyrrolidine (**5**).[19] Partial reduction of the lactam with lithium triethylborohydride and trapping of the resulting iminium ion with potassium cyanide yields chiral aminonitrile **6** in moderate yield but with high diastereoselectivity.

Scheme 1. Derivatization of Arylation Products.[a]



[a] Conditions: (a) CAN, MeCN/H_2O, 0 °C, 30 min, 73% yield; (b) LAH, Et_2O, 0 °C to 23 °C, 16 h, 93% yield; (c) $LiBEt_3H$, –78 °C to 23 °C, then AcOH, KCN, 0 °C, 5 h, 43% yield, 93:7 dr.

In conclusion, we have developed a protocol for the first transition metal-catalyzed enantioselective α-arylation of γ-lactams. Two related procedures were developed for this transformation, allowing for the use of either aryl chlorides or bromides as electrophiles. We are able to construct α-quaternary stereocenters in good yield and high enantiomeric excess (up to 91% yield and 97% ee). Asymmetry is induced through the use of a chiral, dialkyl bisphosphine ligand that generates a Pd/ligand complex that is stable under strongly basic conditions and elevated temperatures. Critical to the development of these conditions was also the identification of an appropriate base and electrophile combination. We found that a broad range of substitution is tolerated on either coupling partner. We also demonstrated that these α-quaternary lactams can be efficiently converted to a number of different enantioenriched nitrogen containing heterocyclic building blocks via product derivatizations. Finally, we were pleased to find that in preliminary studies our conditions can be applied to the enantioselective α-vinylation of lactams.[20] A more extensive report of these investigations will be disclosed in due course.

Acknowledgements

The NIH-NIGMS (R01GM080269) and Caltech are thanked for support of our research program. C. I. Jette thanks the National Science Foundation for a predoctoral fellowship. I. Geibel acknowledges the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship (GE 3082/1-1). H.S. thanks Shionogi & Co., Ltd. for a research grant and fellowship. J. B. Morgan acknowledges the University of North Carolina Wilmington for research reassignment and travel funds. Dr. Scott Virgil (Caltech) is thanked for instrumentation and SFC assistance.

Keywords: Palladium • α-arylation • Nitrogen heterocycles • quaternary stereocenters • asymmetric catalysis

[1] For pyrrolidine-containing alkaloids, see: (a) T. J. Donohoe, C. J. R. Bataille, G. W. Churchill, *Annu. Rep. Prog. Chem., Sect. B* **2006**, *102*, 98–122. (b) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem*. **2003**, *19*, 3693–3712.

[2] For recent reviews on the synthesis of pyrrolidinone containing alkaloids: (a) Y. Long-Wu; C. Shu, F. Gagosz, *Org. Biomol. Chem.* **2014**, *12*, 1833–1845. (b) F. Rivas, T. Ling, *Org. Prep. Proced. Int.* **2016**, *48*, 254−295.

[3] For some examples of biologically active pyrrolidines, see: (a) A. P. Guzikowski, A. P. Tamiz, M. Acosta-Burruel, S. Hong- Bae, S. X. Cai, J. E. Hawkinson, J. F. W. Keana, S. R. Kesten, C. T. Shipp, M. Tran, E. R. Whittemore, R. M. Woodward, J. L. Wright, Z. L. Zhou, *J. Med. Chem.* **2000**, *43*, 984–994. (b) C. L. Lynch, J. J. Hale, R. J. Budhu, A. L. Gentry, S. G. Mills, K.T. Chapman, M. MacCoss, L. Malkowitz, M. S. Springer, S. L. Gould, J. A. DeMartino, S. J. Siciliano, M. A. Cascieri, A. Carella, G. Carver, K. Holmes, W. A. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Miller, E. A. Emini, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001–3004. (c) M. E. Hensler, G. Bernstein, V. Nizet, A. Nefzi, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5073–5079. (d) X. Li, J. Li, *Mini-Rev. Med. Chem.* **2010**, *10*, 794–805. (e) K. W. Lexa, H. A. Carlson, *Proteins* **2011**, *79*, 2282–2290. (f) L. R. Whitby, Y. Ando, V. Setola, P. K. Vogt, B. L. Roth, D. L. Boger, *J. Am. Chem. Soc.* **2011**, *133*, 10184–10194. (g) A. Raghuraman, E. Ko, L. M. Perez, T. R. Ioerger, K. Burgess, *J. Am. Chem. Soc.* **2011**, *133*, 12350–12353. For select examples of biologically active pyrrolidinones see: (a) J. Caruano, G.G. Muccioli, R. Robiette, *Org. Biomol. Chem.*, **2016**, *14*, 10134–10156. (b) J. J. –W. Duan, L. Chen, Z. R. Wasserman, Z. Lu, R. –Q. Liu, M. B. Covington, M. Qian, K. D. Hardman, R. L. Magolda, R. C. Newton, D. D. Christ, R. R. Wexler, C. P. Decicco, *J. Med. Chem.* **2002**, *45*, 4954–4957.

[4] M. Teodorescu, M. Bercea, *Polym Plast Technol Eng.* **2015**, *54*, 923–943.

[5] (a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748. b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. c) B. List, *Synlett* **2001**, *11*, 1675–1686. d) B. List, *Tetrahedron* **2002**, *58*, 5573–5590. e) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557. f) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591. (g) S. Zhang, W. Wang, Q.–L. Zhou, Privileged Chiral Ligands and Catalysts; Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 409−439. (h) A. J. B. Watson, D. W. C. MacMillan, I. Ojima, Enantioselective Organocatalysis Involving Iminium, Enamine SOMO and Photoredox Activation. In Catalytic Asymmetric Synthesis, 3rd ed.; Ed.; Wiley & Sons: Hoboken, NJ, 2010; pp 39−57. (i) C. A. Caputo, N. D. Jones, *Dalton Trans.* **2007**, 4627.

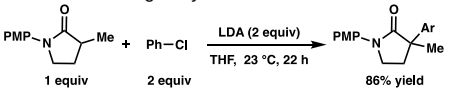
[6] D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2012**, *4*, 130–133.

[7] M. Hayashi, S. Bachman, S. Hashimoto, C. C. Eichman, B. M. Stoltz, *J. Am. Chem. Soc*. **2016**, 138, 8997–9000

[8] L.–N. Wang, Q. Cui, Z.–X. Yu, *J. Org. Chem.* **2016**, *81*, 10165–10171.

[9] (a) J. D. Stewart, S. C. Fields, K. S. Kochhar, H. W. Pinnick, *J. Org. Chem.* **1987**, *52*, 2110–2113. (b) K. H. Shaughnessy, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546–6553.

[10] In the presence of strong base and no transition-metal catalyst, the product was formed in good yield at 23 °C:



[11] (a) M. J. Durbin, M. C. Willis, *Org. Lett.*, **2008**, *10*, 1413–1415. (b) R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 9613–9620. (c) C.–K. Mai, M. F. Sammons, T. Sammakia, *Org. Lett.* **2010**, *12*, 2306–2309. (d) E. Koch, R. Takise, A. Studer, J. Yamaguchi, K. Itami, *Chem. Commun.* **2015**, *51*, 855–857. (e) J. Duan, F. Y. A Kwong, *J. Org. Chem.* **2017**, *82*, 6468–6473. (f) P. K. R. Panyam, B. Ugale, T. Gandhi, *J. Org. Chem.* **2018**, *83*, 7622–7632. (g) A. Vignesh, W. Kaminsky, N. Dharmaraj, *Chem. Cat. Chem.* **2017**, *9*, 910–914. (h) P. Li, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 6520–6524. *Angew. Chem. Int. Ed.* **2011**, *50*, 6396–6400. For

enantioselective examples see: (i) A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901. (j) Y. Jin, M. Chen, S. Ge, J. F. Hartwig, *Org. Lett.* **2017**, *19*, 1390–1393. For examples of Pd-catalyzed enantioselective α-arylation to form quaternary centers see: (k) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. (l) J. García-Fortanet, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 8108–8111. *Angew. Chem.* **2008**, *120*, 8228–8231. (m) X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

[12] (a) J. Cossy, A. de Filippis, D. G. Pardo, *Org. Lett.* **2003**, *5*, 3037–3039. (b) A. de Filippis, D. G. Pardo, J. Cossy, *Tetrahedron*, **2004**, *60*, 9757–9767. *Tetrahedron*, **2004**, *60*, 9757–9767. (c) J. Cossy, A. de Filippis, D. G. Pardo, *Synlett*, **2003**, *14*, 2171–2174.

[13] An additional 22 ligands were examined under slightly modified conditions. See supporting information for details.

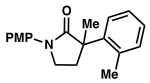
[14] J. E. Marcone, K. G. Moloy, *J. Am. Chem. Soc.* **1998**, *120*, 8527–8528.

[15] (a) F. E. Goodson, T. I. Wallow, B. M. Novak, *J. Am. Chem. Soc.* 1997, 119, 12441–12453. (b) D. K. Morita, J. K. Stille, J. R. Norton, *J. Am. Chem. Soc.* **1995**, *117*, 8576–8581.

[16] We obtained a crystal structure of Pd/**L4** complex. See supporting information for details.

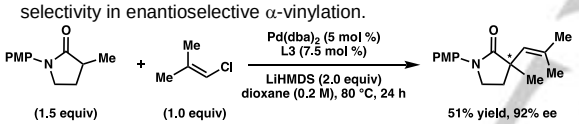
[17] A control experiment omitting the Pd catalyst revealed a background reaction by which the same product was formed in 80% yield.

[18] Using Method A, the corresponding *ortho*-methyl product was obtained in only 14% yield.



[19] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.

[20] Preliminary experiments showed diminished reactivity but good selectivity in enantioselective α-vinylation.



10.1002/anie.201814475

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Layout 2:

COMMUNICATION

We report the first Pd-catalyzed enantioselective arylation of α-substituted γ-lactams. Two sets of conditions were developed for this transformation, allowing for the use of either aryl chlorides or bromides as electrophiles. Utilizing commercially available ferrocelane ligands, we have been able to construct α-quaternary centers in good yields (up to 91% yield) and high enantioselectivities (up to 97% ee).

Carina I. Jette, Irina Geibel, Shoshana Bachman, Masaki Hayashi, Shunya Sakurai, Hideki Shimizu, Jeremy B. Morgan, Brian M. Stoltz**

Page No. – Page No.

Palladium-Catalyzed Construction of Quaternary Stereocenters by Enantioselective Arylation of γ-Lactams with Aryl Chlorides and Bromides