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Letter

Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to α,β-Unsaturated Lactams: Enantioselective Construction of All-Carbon Quaternary Stereocenters in Saturated Nitrogen-Containing Heterocycles

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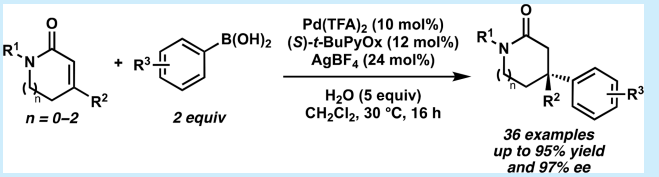
ABSTRACT: Stereogenic nitrogen-containing heterocycles are ubiquitous in natural products and pharmaceutical compounds, but methods for their enantioselective construction have remained elusive. We report a general method for the asymmetric conjugate addition of arylboronic acids to β-alkyl/aryl α,β-unsaturated lactams that affords chiral β,β-disubstituted lactams. The transformation is operationally simple and air- and moisture-tolerant and uses a commercially available (*S*)-*t*-Bu-PyOx ligand. The method is high-yielding (up to 95% yield) and enantioselective (up to 97% ee) for a wide range of arylboronic acids and α,β-unsaturated lactams, including those with different ring sizes.



Asymmetric catalysis has seen significant applications in complex molecule synthesis, enabling the facile preparation of valuable enantioenriched synthetic building blocks from prochiral and racemic starting materials, especially those containing all-carbon quaternary centers.[1] The enantioselective construction of all-carbon quaternary centers, while challenging due to the inherent steric demand, has become an important area of research, owing to the widespread presence of these structural motifs in natural products.[2] Moreover, the incorporation of C(sp^3) stereocenters into small-molecule drugs has been correlated with the clinical success of drug candidates.[3] One approach toward synthesizing stereogenic centers is through asymmetric conjugate addition,[4] which can be catalyzed by a wide range of transition metals including copper,[5] manganese,[6] nickel,[7] scandium,[8] and palladium.[9] While many of these methodologies require the use of air- and moisture-sensitive organometallic reagents, strongly basic nucleophiles, or a combination thereof, palladium catalysis enables the use of bench-stable boronic acids and water cosolvents.[9] The first Pd-catalyzed enantioselective conjugate addition of arylboronic acids to cyclic β-alkyl enones was reported by our group in 2011 and involved the use of a chiral pyridinooxazoline (PyOx) ligand (Scheme 1A).[10] Soon after, the substrate scope was broadened to include lactones (Scheme 1B),[11] chromones,[12] 4-quinolones,[13] and cyclic β-aryl enones.[14] While access to racemic β,β-disubstituted lactams has been demonstrated,[15] there were limited examples of the enantioselective construction of lactams bearing all-carbon β-quaternary stereocenters when we commenced our investigations.

N-heterocycles, common in natural products,[16] pharmaceuticals,[17] and new materials,[18] can be accessed from lactams through exhaustive reduction, which does not allow the incorporation of quaternary centers.[19] Currently, there is a lack of stereochemical complexity in most *N*-heterocycles in marketed drugs partly due to a lack of methods for the incorporation of stereogenic centers.[20] In light of this, chiral lactams containing all-carbon β-quaternary centers would serve as synthetically valuable precursors to enantiopure γ,γ-disubstituted saturated *N*-heterocycles, allowing synthetic chemists to "escape from the flatland".[20] Toward the end of our studies, Baek et al. became the first to report a Pd-catalyzed asymmetric conjugate addition of arylboronic acids to α,β-unsaturated lactams (Scheme 1C).[21] Herein, we report the development of a complementary palladium-catalyzed asymmetric conjugate addition of arylboronic acids to α,β-unsaturated lactams to afford β-quaternary stereogenic centers in high yield and enantioselectivity, under air- and moisture-tolerant conditions and at near-ambient temperature (Scheme 1D).

We first investigated the asymmetric conjugate addition of phenylboronic acid (**2**) to *N*-tosyl protected lactam **1** utilizing conditions reported for cyclic enones by our group (entry 1, Table 1).[10a] An array of chiral ligands were studied (Table S1, see Supporting Information), and (*S*)-*t*-BuPyOx (**4**)[22] was found to provide the highest level of enantioselectivity. Pairing

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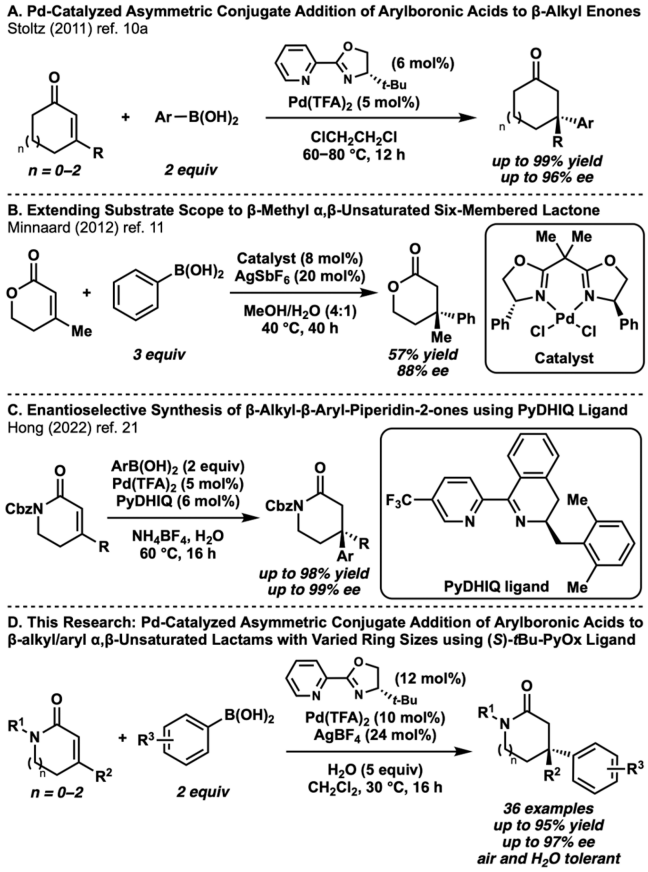
Scheme 1. Construction of All-Carbon Quaternary Centers in Cyclic Ketones, Lactones, and Lactams via Pd-Catalyzed Conjugate Addition

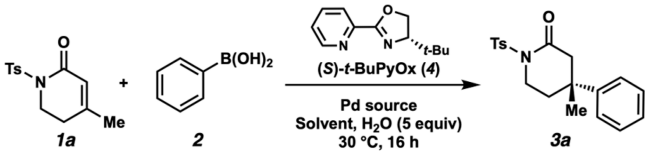


ligand **4** with the aqueous conditions developed by the Stanley group[14a] afforded lactam **3** with low enantioselectivity and yield (entry 2, Table 1), likely due to ligand hydrolysis at high temperature.

The effects of solvent and reaction temperature were examined (Table S2, see Supporting Information). Replacing 1,2-dichloroethane (DCE) with chloroform as the solvent and lowering the reaction temperature (from 60 to 40 °C) led to improved enantioselectivity (Entries 3–4, Table 1). Dichloromethane was identified as the optimal solvent (entry 5, Table 1), providing product **3a** in 68% yield with 72% ee. The enantioselectivity was improved by lowering the temperature to 30 °C with a longer reaction time (entry 6, Table 1). Addition of silver(I) additives, which were reported to aid in precatalyst activation through counterion abstraction,[10a,11] improved the reaction yield (>99%, entries 7 and 11, Table 1) while maintaining high enantioselectivity (80–82% ee); silver tetrafluoroborate, $AgBF_4$, provided the highest yield (>99%) and excellent enantioselectivity (82% ee) from the silver(I) salts tested (entries 7, 10, 11 in Table 1; Table S3 in Supporting Information). An array of palladium(II) precatalysts were competent in the presence of a silver(I) additive (entries 7–9, Table 1; also see Table S4 in Supporting Information), with $Pd(TFA)_2$ providing the highest yield (>99%) and enantioselectivity (82% ee) in the presence of air and 5 equivalents of water (entry 11).[23]

The scope of the reaction, with respect to the *N*-protecting groups, was examined (Table 2). The method was found to be compatible with various *N*-protecting groups such as sulfonyl

Table 1. Optimization of Reaction Conditions[a]



Entry	Pd source	Solvent	Variations from standard conditions	Yield (%)[b]	ee (%)[c]
1	$Pd(TFA)_2$	DCE	NH_4PF_6 (30 mol %), O_2,[d] 60 °C	49	41
2	$Pd(TFA)_2$	H_2O	Na(TFA) (20 mol %), 100 °C	9	23
3	$Pd(TFA)_2$	$CHCl_3$	NH_4PF_6 (30 mol %), O_2, 60 °C	25	61
4	$Pd(TFA)_2$	$CHCl_3$	NH_4PF_6 (30 mol %), O_2, 40 °C	25	73
5	$Pd(TFA)_2$	CH_2Cl_2	NH_4PF_6 (30 mol %), O_2, 40 °C	68	72
6	$Pd(TFA)_2$	CH_2Cl_2	NH_4PF_6 (30 mol %), O_2, 40 h	68	78
7	$Pd(TFA)_2$	CH_2Cl_2	AgOTf (24 mol %)	>99	80
8	$Pd(OAc)_2$	CH_2Cl_2	AgOTf (24 mol %)	92	64
9	$Pd(MeCN)_2Cl_2$	CH_2Cl_2	AgOTf (24 mol %)	45	71
10	$Pd(TFA)_2$	CH_2Cl_2	AgOAc (24 mol %)	47	86
11	$Pd(TFA)_2$	CH_2Cl_2	$AgBF_4$ (24 mol %)	>99	82

[a]Standard conditions: Reactions were performed with phenylboronic acid **2** (0.08 mmol, 4 equiv), lactam **1** (0.02 mmol), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (**4**, 12 mol %), and H_2O (5 equiv) in the given solvent (0.16 mL) at 30 °C for 16 h. [b]Yield was determined by ^1H NMR with 1,3,5-trimethoxybenzene internal standard. [c]ee was determined by chiral SFC and absolute stereochemistry by VCD. [d]"O_2" ≡ Reaction under 1 atm O_2.[24]

(**3a**, >99% yield, 82% ee) and benzoyl (**3b–d**, 65–90% yields, 79–81% ee). Substrates containing Teoc (**3m**) and Boc (**3n**) groups provided lower yields potentially due to the inherent steric bulk. Notably, high enantioselectivity (89% ee), despite a diminished yield (14%), was observed for the unprotected lactam (**3o**), which is uncommon due to potentially deleterious substrate coordination.[23] The Troc protecting group afforded the highest yield (**3f**) and excellent enantioselectivity, so substrate **1f** was used in subsequent substrate scope explorations.

To investigate the nucleophile scope, a range of arylboronic acids were evaluated (Table 3). Arylboronic acids with electron-withdrawing *para*-substituents (**5a–d**) generally afforded the desired product in high yields (61–95%) and enantioselectivities (80–96%). Electron-withdrawing groups on the boronic acid reaction partner included halides (**5a–b**), a trifluoromethyl group (**5c**), and a ketone (**5d**). Switching to arylboronic acids bearing electron-donating *para*-substituents (**5e–h**) lowered the reaction yield (0–79%) and enantioselectivity (40–56% ee), with electron-rich aniline **4h** affording none of the desired product **5h**. Meanwhile, *meta*-substituted arylboronic acids, with either electron-donating or electron-withdrawing substituents, are compatible with the catalytic conditions and furnished the desired products in 68–94% yield and 76–93% ee (**5i–k**). In contrast, *ortho*-substituents on the arylboronic acid led to diminished yields and stereoselectivity (**5l–n**).[25] In general, we found the nucleophile scope to be largely consistent with our group's previous reports on the analogous cyclic enone system.[10a]

Finally, *α,β*-unsaturated lactams varying in ring size and *β*-substitution pattern were examined (Table 4). The reaction

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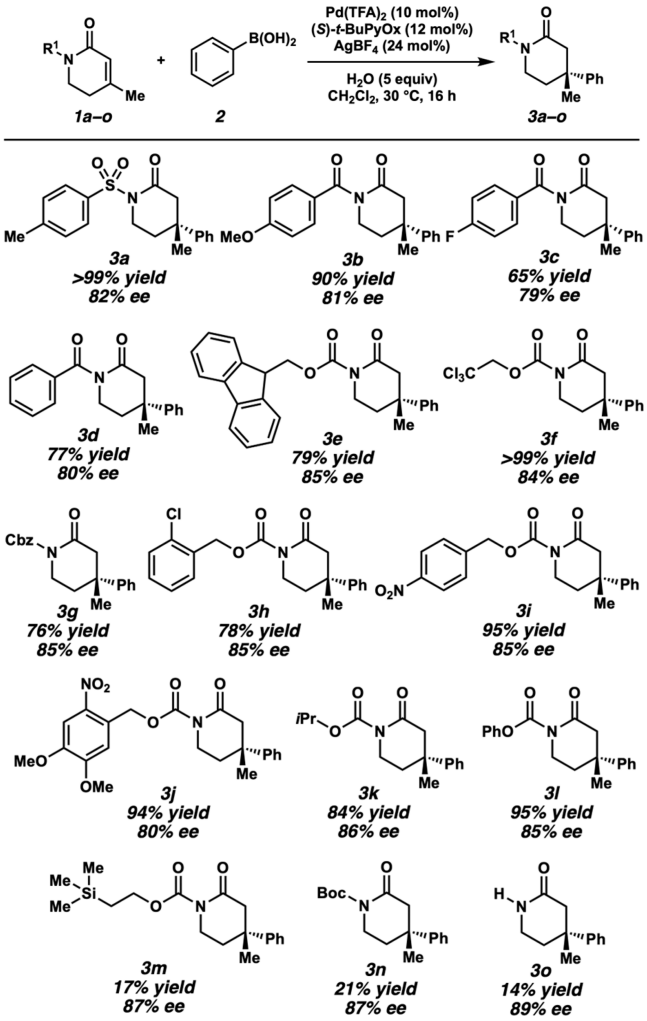
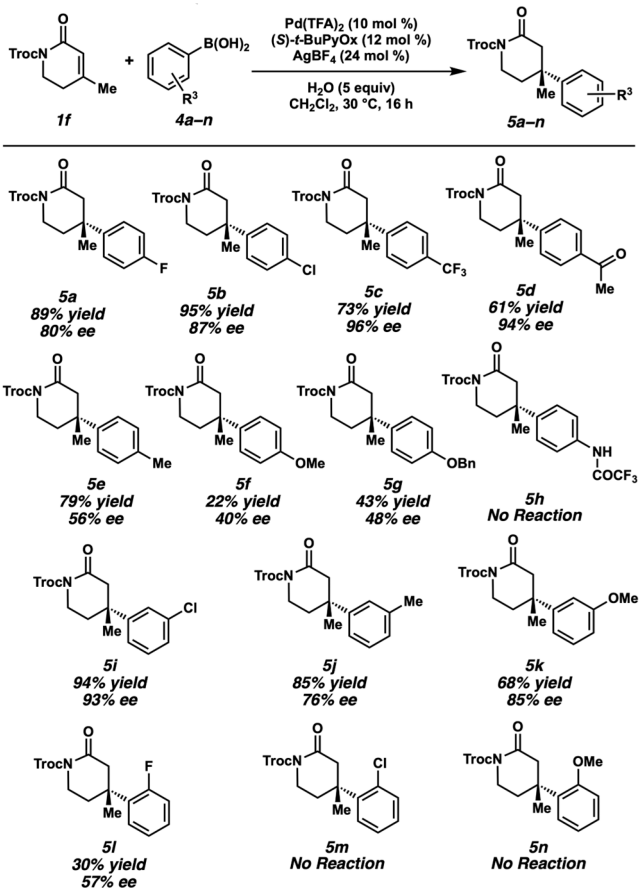
Table 2. Substrate Scope: Variation of the Lactam *N*-Protecting Group. Addition of Phenylboronic Acid to Lactams (1a−o) with Different *N*-Protecting Groups[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.08 mmol, 4 equiv), lactams **1a−o** (0.02 mmol), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), $AgBF_4$ (24 mol %), H_2O (5 equiv) in CH_2Cl_2 (0.16 mL) at 30 °C for 16 h. Yield was determined by ^1H NMR relative to 1,3,5-trimethoxybenzene internal standard. ee was determined by chiral SFC.

Table 3. Investigation of the Nucleophile Scope: Addition of Different Arylboronic Acids (4a−n) to Lactam 1f[a]



[a]Conditions: Reactions were performed with phenylboronic acid **4a−n** (0.20 mmol, 2.0 equiv), lactam **1f** (0.10 mmol), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), $AgBF_4$ (24 mol %), H_2O (0.50 mmol, 5.0 equiv) in CH_2Cl_2 (0.80 mL) at 30 °C for 16 h. Yields are of isolated products after column chromatography. ee was determined by chiral SFC.

remained robust for five- and seven-membered ring substrates, furnishing the corresponding products in excellent enantioselectivity and moderate to excellent yield (**7a**,**b**).[26] To our knowledge, these represent the only examples of asymmetric construction of *β*-quaternary centers in five- and seven-membered lactams through enantioselective conjugate addition of arylboronic acids to *α*,*β*-unsaturated lactams, which are valuable synthetic building blocks for *N*-heterocycles.

Reactions with *α*,*β*-unsaturated lactams bearing other *β*-alkyl substituents, such as *n*-butyl and benzyl (**7c**,**d**), delivered the respective lactam products in high yield (76−86%) and enantioselectivity (83−90% ee). In addition to linear *β*-alkyl substitution, isopropyl (**6e**), cyclobutyl (**6f**), and cyclohexyl (**6g**) *β*-alkyl-branched substrates afforded products (**7e−g**) in good yields (58−91%) and enantioselectivities (61−84% ee). Moreover, preliminary studies demonstrated that *α*,*β*-unsaturated lactams bearing a *β*-aryl substituent (**7h**) were also compatible with the developed conditions. The reaction produced the desired *β*,*β*-diaryl lactam product with high enantioselectivity (90% ee) and good yield (58%). In comparison, the previous Pd-catalyzed conditions for asymmetric conjugate addition to cyclic enones developed by our group did not provide access to *β*,*β*-diaryl cyclic ketones.[27]

Toward the end of our studies, Baek et al. published the first method for Pd-catalyzed asymmetric conjugate addition of arylboronic acids to *α*,*β*-unsaturated lactams.[21] In comparison, our method offers several complementary advances, including (1) the utilization of a commercially available chiral ligand (i.e., (*S*)-*t*-BuPyOx) that can also be synthesized on scale from simple starting materials,[28,29] (2) the robustness demonstrated in the asymmetric synthesis of *β*,*β*-disubstituted lactams varying in ring size and *β*-alkyl and *β*-aryl substitution patterns, (3) tolerance of various *N*-protecting groups, and (4) use of near-ambient temperatures (i.e., instead of 60−70 °C).

In summary, we have developed a palladium-catalyzed asymmetric conjugate addition of arylboronic acids to *β*-substituted *α*,*β*-unsaturated lactams for the asymmetric construction of all-carbon quaternary stereocenters in nitrogen-containing heterocycles. The transformation provides access to a diverse array of lactams bearing new all-carbon quaternary centers in up to 95% yield and 97% ee. This serves

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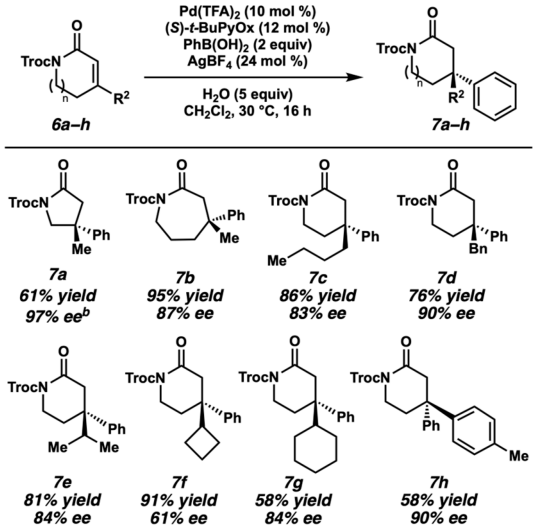
Table 4. Asymmetric Synthesis of β,β-Disubstituted Lactams[a]



[a]Conditions: Reactions were performed with phenylboronic acid (0.20 mmol, 2.0 equiv), lactams **6a–h** (0.10 mmol), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), $AgBF_4$ (24 mol %), H_2O (0.5 mmol, 5 equiv) in CH_2Cl_2 (0.16 mL) at 30 °C for 16 h. Yields are of isolated products after column chromatography. ee determined by chiral SFC. [b]Reaction time is 47 h.

as the first general method for the asymmetric conjugate addition of arylboronic acids to five-, six-, and seven-membered α,β-unsaturated lactams, providing products with high enantioselectivity. Furthermore, both β-alkyl and β-aryl α,β-unsaturated lactam substrates participate in the reaction with excellent enantioinduction. The reaction applies to lactams of different ring sizes and displays broad functional group tolerance, compatible with various *N*-protecting groups, β-substituents, as well as arylboronic acids with various substitution patterns. The transformation proceeds at near-ambient temperature and is air- and moisture-tolerant. Key to the success of this reaction is the readily available chiral ligand, (*S*)-*t*-BuPyOx (**4**), rendering this catalytic system an operationally simple and practical method for enantioselective construction of lactams bearing new all-carbon quaternary stereocenters. Continuing studies of this method and its application in the context of natural product synthesis are currently ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02064.

Experimental details and NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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