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Asymmetric Synthesis of γ-Lactams Containing α,β-Contiguous Stereocenters via Pd(II)-Catalyzed Cascade Methylene C(sp^3)−H Alkenylation/Aza-Wacker Cyclization

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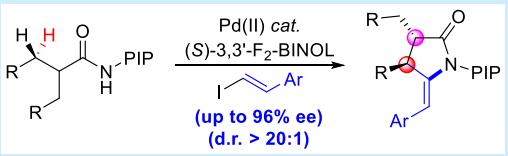
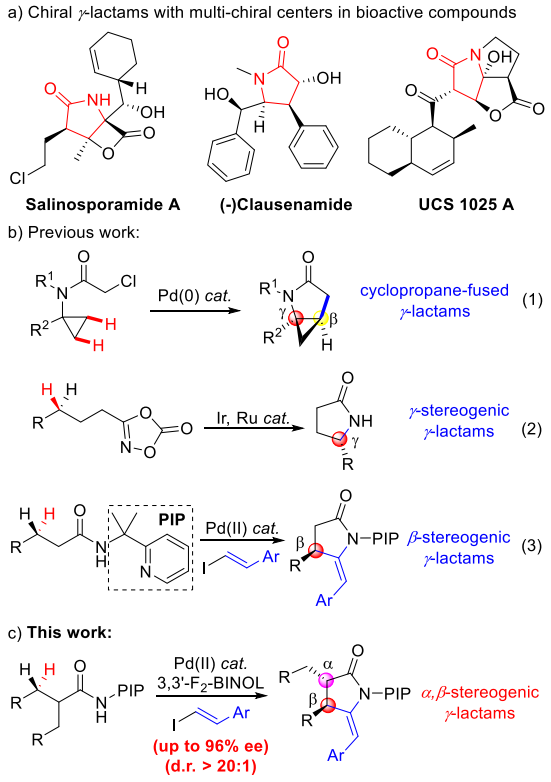
ABSTRACT: γ-Lactam containing α,β-contiguous stereogenic centers stands out as a pivotal motif in various bioactive compounds, while its efficient synthesis still needs to be enhanced. Herein, an asymmetric C−H activation strategy for accessing α,β-stereospecific γ-lactams in good yields (≤79%) with high enantio- and diastereoselectivities (≤96% ee and >20:1 dr) was described, which serves as an effective supplement to the existing strategies.



Chiral γ-lactams occur widely in natural products and bioactive compounds, among which those with contiguous stereogenic centers are significantly structurally important and pose synthetic challenges (Scheme 1a).[1] Early efforts relying on conventional methods mainly involved construction of γ-lactams with a single chiral center,[2] while syntheses of γ-lactams bearing contiguous stereogenic centers have been less explored.[3] Despite the fact that these elegant precedents have provided diverse approaches to afford a series of γ-lactams, considering the significance of such frameworks, we sought to develop an alternative strategy based on enantioselective C(sp^3)−H functionalization to construct γ-lactams with contiguous stereogenic centers from readily available aliphatic carboxylic acids.

Scheme 1. Synthesis of Chiral γ-Lactams via an Asymmetric C(sp^3)−H Bond Functionalization Strategy



In the past few years, tremendous effort has been devoted to the pursuit of new approaches to chiral γ-lactams via asymmetric C−H functionalization.[4−7] In 2015, Cramer and co-workers reported the synthesis of cyclopropane-fused γ-lactams via Pd(0)-catalyzed asymmetric C−H functionalization (Scheme 1b, eq 1).[5] Recently, Chang,[6a] Yu,[6b] Chen,[6c] and Meggers[6d] disclosed the intramolecular C−H amidation of dioxazolones via metallonitrene (Ir and Ru) insertion to provide the corresponding chiral γ-lactams with a γ-stereocenter (Scheme 1b, eq 2). Later, our group developed a Pd(II)-catalyzed enantioselective C−H alkenylation/aza-Wacker cyclization to construct γ-lactams with a β-stereocenter (Scheme 1b, eq 3).[7] Despite these advances, one-step formation of γ-lactams containing α,β-contiguous stereogenic centers via a C−H functionalization strategy is underdeveloped.

Recently, our group has been engaged in developing efficient protocols for the enantioselective functionalization of unbiased methylene C(sp^3)−H bonds.[8−10] We have successfully addressed the challenges of enantio-, chemo-, and diaster-

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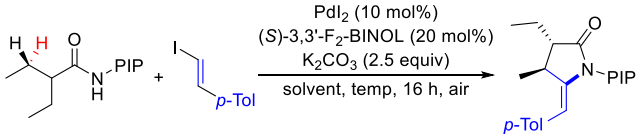
eoselective differentiation of chemically identical quadruple C(sp^3)−H bonds, enabling the simultaneous control of α- and β-chirality to access α,β-stereogenic acyclic aliphatic amides.[8c] In light of this achievement, along with the synthesis of β-stereogenic γ-lactams,[7] we envisioned that the enantioselective C(sp^3)−H alkenylation of aliphatic amides with alkenylation partners followed by intramolecular cyclization through *syn*-aminopalladation/β-H elimination might be feasible to access the target structures. Herein, we report the construction of chiral γ-lactams featuring contiguous α,β-stereocenters with high enantio- and diastereoselectivities via desymmetric C−H alkenylation of *gem*-dialkyl C(sp^3)−H bonds, followed by aza-Wacker cyclization cascade (Scheme 1c).

Our investigation was initiated by testing the reaction between 2-pyridinylisopropyl (PIP)-derived 2-ethylbutanoic amide (**1a**)[11,12] and (*E*)-1-(2-iodovinyl)-4-methylbenzene (**2b**), in the presence of PdI_2 as a catalyst, (*S*)-3,3′-F_2-BINOL as a chiral ligand, and K_2CO_3 as a base (Table 1). To

Table 1. Optimization of the Reaction Conditions[a]



1a **2b** **3b**

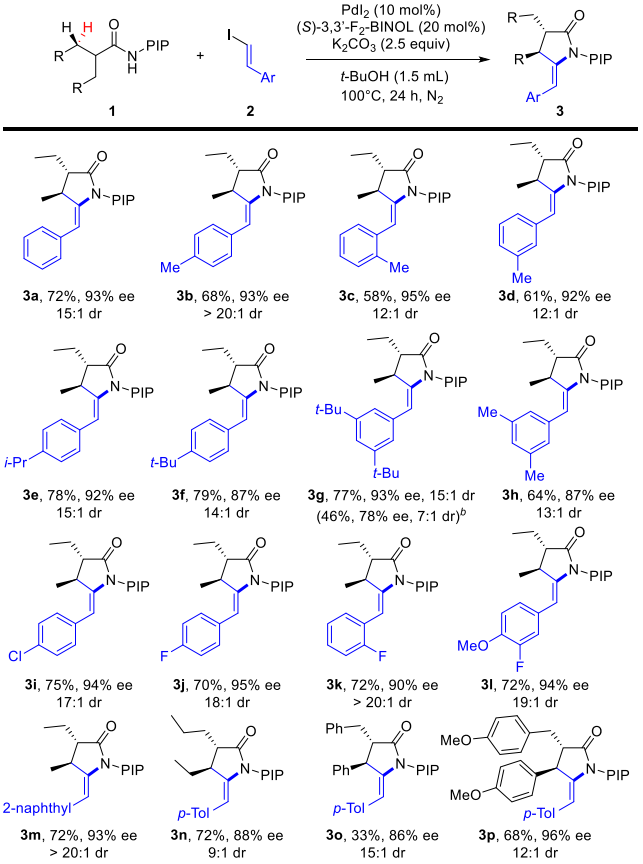
entry	solvent (mL)	temp (°C)	yield (%)[b]	ee (%)[c]	dr[b]
1	MeCN (1.0)	110	32	7	11:1
2	1,4-dioxane (1.0)	110	25	63	11:1
3	*t*-BuOH (1.0)	110	44	90	>20:1
4	*t*-BuOH (1.0)	100	41	91	>20:1
5	*t*-BuOH (1.0)	90	41	90	>20:1
6	*t*-BuOH (1.5)	100	44	94	>20:1
7[d]	*t*-BuOH (1.5)	100	62	93	>20:1
8[e]	*t*-BuOH (1.5)	100	68[f]	93	>20:1

[a]Reaction conditions: **1a** (0.10 mmol), **2b** (2.0 equiv), PdI_2 (10 mol %), K_2CO_3 (2.5 equiv), and (*S*)-3,3′-F_2-BINOL (20 mol %) in a solvent at a certain temperature for 16 h under air. [b]The yields and dr values were determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as the internal standard. [c]The ee value was determined by HPLC. [d]With 3.0 equiv of **2b**. [e]With 3.0 equiv of **2b**, N_2, 24 h. [f]Isolated yield.

our delight, *t*-BuOH proved to be an efficient solvent for ensuring a moderate yield (44%) and satisfactory stereocontrol (90% ee, >20:1 dr), whereas inferior results were obtained by applying other solvents (entries 1−3; see the Supporting Information for details). Adjusting the temperature had little effect on the reaction (entries 3−5), while decreasing the concentration and increasing the number of equivalents of alkenylation reagent improved both the enantioselectivity and yield (entries 6 and 7). The reaction proceeded better under a N_2 atmosphere with a prolonged reaction time (24 h), giving **3b** in 68% isolated yield with 93% ee along with a diastereoselective rate up to >20:1.

With the optimized reaction conditions in hand, the scope of vinyl iodides was examined (Scheme 2). Aryl vinyl iodides bearing electron-donating groups reacted well, affording the desired chiral γ-lactams (**3a**−**3h** and **3m**) with high levels of enantio- and diastereoselectivity (87−95% ee, 12:1 to >20:1 dr). In addition, vinyl iodides containing electron-withdrawing groups, such as chloro and fluoro, were well tolerated and the corresponding products (**3i**−**3l**) were obtained with high

Scheme 2. Scope of Vinyl Iodides and Aliphatic Amides[a]



[a]Reaction conditions: **1** (0.10 mmol), **2** (3.0 equiv), PdI_2 (10 mol %), K_2CO_3 (2.5 equiv), and (*S*)-3,3′-F_2-BINOL (20 mol %) in *t*-BuOH (1.5 mL) at 100 °C under N_2 for 24 h. The dr values were determined by ^{1}H NMR analysis of the crude product. The ee value was determined by HPLC. [b]On a 1 mmol scale.

enantiocontrol (90−95% ee) and slightly higher diastereoselective rates (17:1 to >20:1 dr), compared with those of most of the electron-rich ones. However, no desired product was observed when using (*E*)-1-(2-iodovinyl)-4-nitrobenzene as a coupling partner. The compatibility of *gem*-dialkyl aliphatic amides was then explored. An amide with a *gem*-dipropyl group was transformed into γ-lactam (**3n**) in good yield (72%) with good enantioselectivity (88% ee) and moderate diastereoselectivity (9:1 dr), while the reaction of dibenzyl-substituted amide led to a dramatically decreased yield (**3o**, 33% yield, 86% ee, 15:1 dr). Gratifyingly, the introduction of methoxyl groups at the *para* position of phenyl rings on both branches of the substrate gave desired product **3p** in satisfying yield and outstanding stereoselectivity (68% yield, 96% ee, 12:1 dr). The reaction of **1a** (1 mmol) with alkenyl iodide **2g** (3 mmol) led to reduced yield (46%) and enantioselectivity (78% ee). Unfortunately, alkyl vinyl iodides were not tolerated.

To showcase the synthetic potential of this protocol, further transformations were conducted using **3b** as the model substrate (Scheme 3). Upon treatment with hydrazine hydrate in an acidic environment, the directing group could be easily removed and a six-membered cyclic acyl hydrazone **4** was formed in 80% yield with maintained enantioselectivity (93% ee) and diastereoselective rate (>20:1). Meanwhile, the absolute stereochemistry of **4** was confirmed by X-ray crystallographic analysis. **4** could be further reduced with

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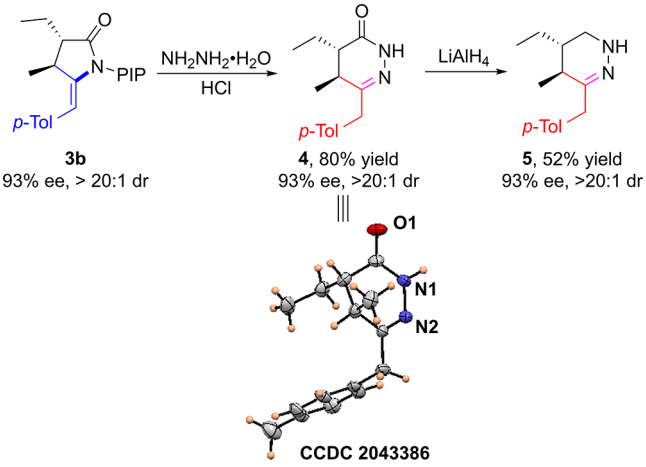
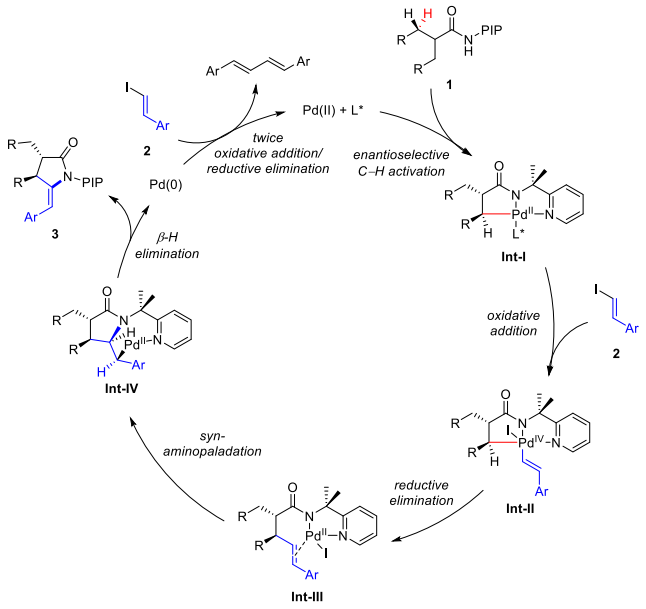
Scheme 3. Synthetic Transformations



excessive $LiAlH_4$, giving chiral tetrahydropyridazine **5** in 52% yield without erosion of the ee or dr value.

On the basis of previous studies,[7] a possible catalytic cycle of this protocol was proposed (Scheme 4). First, enantioselective

Scheme 4. Proposed Catalytic Cycle



cleavage one of the four β-methylene C(sp^3)−H bonds with the aid of chiral ligand 3,3′-F_2-BINOL led to the formation of chiral palladacycle **Int-I**. Oxidative addition of vinyl iodide **2** onto **Int-I** gave Pd(IV) species **Int-II**, which underwent reductive elimination to generate alkenylation product **Int-III**. The coordination of the amide and alkene to palladium facilitated the intramolecular *syn*-aminopalladation to give **Int-IV**. β-H elimination gave chiral γ-lactam **3**. Finally, the Pd(0) species was reoxidized to Pd(II) by consuming 2 equiv of vinyl iodide **2** to close the catalytic cycle, with the generation of 1,3-diene.[7]

In conclusion, we have developed an efficient method for accessing γ-lactams with α,β-contiguous stereogenic centers via Pd(II)-catalyzed cascade methylene C(sp^3)−H alkenylation/aza-Wacker cyclization assisted by a PIP auxiliary using 3,3′-F_2-BINOL as the chiral ligand. Good yields and high enantio- and diastereoselectivities were successfully achieved. This protocol showcases the fact that C(sp^3)−H desymmetrization of *gem*-dialkyl could be an efficient synthetic tool for synthesizing complicated chiral molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00204.

Experimental details and characterization of all new compounds (PDF)

Accession Codes

CCDC 2043386 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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