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Stereoselective Construction of γ-Lactams via Copper-Catalyzed Borylacylation

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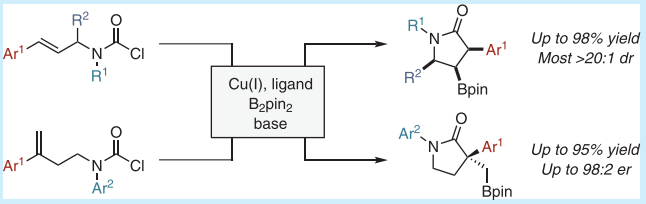
ABSTRACT: A versatile and highly stereoselective borylative cyclization to generate polyfunctionalized γ-lactams has been developed. The stereoselective synthesis of these key ring systems is crucial due to their ubiquity in natural products. We report the diastero- and enantioselective construction of di- and trisubstituted γ-lactam cores, with examples containing an enantioenriched quaternary carbon.



Cyclic amides sit among the privileged motifs in synthetic chemistry. In particular, polyfunctionalized γ-lactams are found in an array of bioactive natural products (Figure 1) and

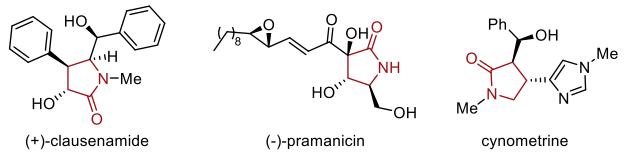
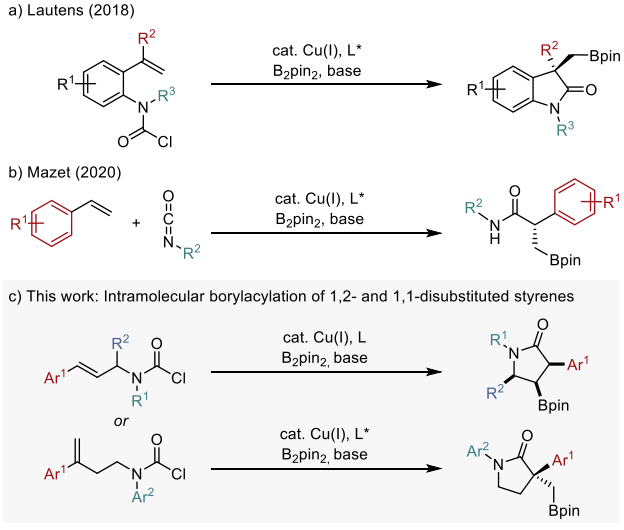


Figure 1. Examples of the γ-lactam core found in natural products.

serve as valuable scaffolds with pharmaceutical applications.[1] Efficient methods to construct these heterocycles is an area of ongoing interest. Despite transition-metal catalysis proving to be a versatile synthetic tool for the construction of chiral γ-lactams, the majority of these methods rely on precious metals and some have limited selectivity and scope.[2,3] Herein, we report a mild, copper-catalyzed intramolecular borylacylation process to access a broad array of differentially substituted γ-lactams. This versatile route enables the utilization of base-metal catalysis to furnish modular variants of γ-lactams.

Borylcupration has emerged as a powerful strategy to difunctionalize π-systems, yielding boronate-containing products capable of undergoing subsequent transformations.[4] These reactions proceed through an initial borylcupration, generating a nucleophilic organocopper species, which can then be intercepted with a variety of electrophiles. Early efforts of Ito[5] and Hoveyda[6] utilized 1,2- and 1,1-disubstituted alkenes in borylation strategies. More recently, Brown[7] and Meng[8] built on these studies and developed methods using acyl electrophiles to intercept the organocopper intermediate.[9] There are limited examples of borylacylation strategies to access highly sought-after amide-containing molecules.[10−14] In 2018, we disclosed the use of carbamoyl chlorides as acylating electrophiles in the copper-catalyzed borylacylation of styrenes to generate chiral oxindoles (Scheme 1a).[10] More recently, the

Scheme 1. Examples of Prior Work in Copper-Catalyzed Borylacylation and the Current Work



Mazet[13] and Tao[14] groups concomitantly reported using exogenous isocyanides to generate secondary amides (Scheme 1b). Notably, utilizing internal alkenes has yet to be fully realized yet represents a potentially valuable pathway toward creating amides with two contiguous stereocenters.

Building on our recent interest in copper-catalyzed cyclization strategies to generate heterocycles,[10,11,15−17] we sought to develop a general route to construct chiral borylated

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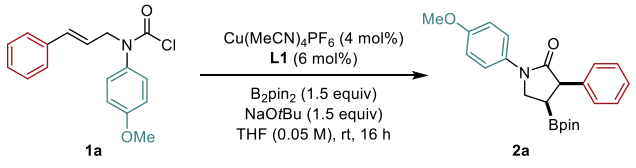
γ-lactams. Utilizing either 1,2- or 1,1-disubstituted alkenes in an intramolecular borylacylation with a tethered carbamoyl chloride would enable the construction of γ-lactams in a stereocontrolled manner (Scheme 1c). Furthermore, the incorporation of a carbon−boron handle would facilitate downstream functionalization adding to the synthetic value of these scaffolds.

Substrate **1a** was the starting point for the investigation, using reaction conditions similar to our previous report.[10] The optimal conditions involve dppe (**L1**) as the ligand and THF as the solvent (Table 1, entry 1). At room temperature, the

Table 1. Optimization of Reaction Conditions



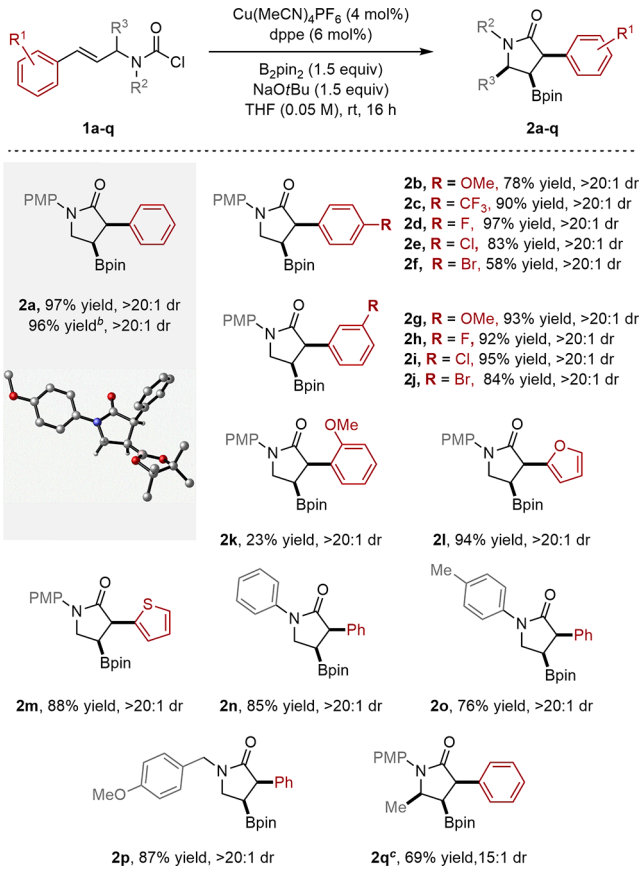
entry	variation of standard condition	yield[a] (%)	dr[b]
1	none	99 (97)	>20:1
2	**L2** instead of **L1**	86	6:1
3	**L3** instead of **L1**	71	3:1
4	**L4** instead of **L1**	65	>20:1
5	KO*t*Bu instead of NaO*t*Bu	80	5:1
6	LiO*t*Bu instead of NaO*t*Bu	94	11:1
7	toluene instead of THF	60	>20:1
8	MTBE instead of THF	84	>20:1
9	1,4-dioxane instead of THF	87	>20:1

[a]NMR yield determined by using 1,3,5-trimethoxybenzene as a standard (isolated yield in parentheses). [b]dr determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

3,4-disubstituted γ-lactam (**2a**) was isolated in 97% yield as a single diastereomer with *syn* configuration (Scheme 2). Other bidentate ligands eroded either selectivity (Table 1, entries 2 and 3) or yield (Table 1, entry 4). Of the commonly employed alkoxide bases, we found that NaO*t*Bu gave the highest diastereoselectivity (Table 1, entries 5 and 6). Toluene delivered the product in slightly lower yield (Table 1, entry 7). Other ethereal solvents such as MTBE or dioxane were suitable; however, improved solubility of the substrate was observed in THF (Table 1, entries 8 and 9). Notably, side-products resulting from direct attack of the borylcopper or alkoxide to the carbamoyl chloride group were not observed. Furthermore, the reaction was amenable to scale-up, as the product could be formed in near identical yield and dr at 2.0 mmol (Scheme 2).

The ability to access diverse 3,4-disubstituted γ-lactams was investigated by examining variation of the styrenyl substituent (Scheme 2). An electron-donating group in the *para* position (**2b**) gave the product in somewhat lower yield. In contrast, electron-withdrawing groups such as trifluoromethyl (**2c**) and fluoro (**2d**) gave the desired product in high yields. A chloro group in the *para* position furnished product **2e** in 83% yield; however, the analogous bromo substrate was less reactive and gave **2f** in significantly lower yield, with incomplete conversion

Scheme 2. Diastereoselective Borylacylation of 1,2-Disubstituted Alkenes[a]



[a]Reactions performed on a 0.2 mmol scale. All reported yields are after isolation; dr determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. PMP = *p*-methoxyphenyl. [b]Reaction performed on a 2.0 mmol scale. [c]Reaction run at 50 °C for 24 h using MTBE instead of THF.

of starting material. Both electron-donating (**2g**) and electron-withdrawing substituents (**2h**) at the *meta* position generated products in excellent yield. Similarly, **2i** was obtained in nearly quantitative yield, while the bromo substrate (**2j**) proved to be less reactive. An *ortho*-methoxy substituent delivered product **2k** in only 23% yield. Substituting a functionalized phenyl ring by a furyl group or thienyl group was successful and generated the respective products **2l** and **2m** in excellent yield.

Modification of the aryl substituent at nitrogen had minor effects on the reaction, with the phenyl (**2n**) and *para*-tolyl (**2o**) groups generating products in 85% and 76% yield, respectively. Beyond *N*-aryl-derived products, a substrate bearing a benzylic substituent on the nitrogen participated in the reaction, delivering **2p** in excellent yield. Attempts to prepare a 3,4,5-trisubstituted γ-lactam revealed that the cyclization was more sluggish, requiring elevated temperature and prolonged reaction time. Following optimization, the all-*syn* trisubstituted product **2q** was formed in 69% yield while maintaining high diastereoselectivity (see the Supporting Information for details). Preliminary investigations of an enantioselective variant revealed the highest asymmetric induction with the Josiphos ligand **L5**, which generated **3n** in 83.5:16.5 er (Scheme 3). Further optimization is needed.

We applied similar conditions to 1,1-disubstituted alkene-tethered carbamoyl chloride (**3a**) to provide the 3,3-

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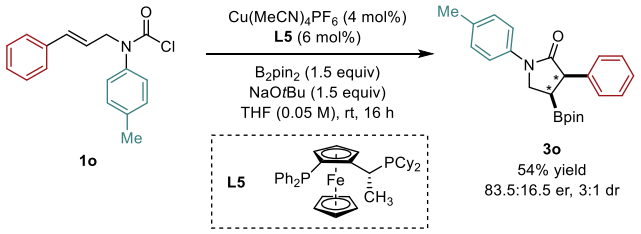
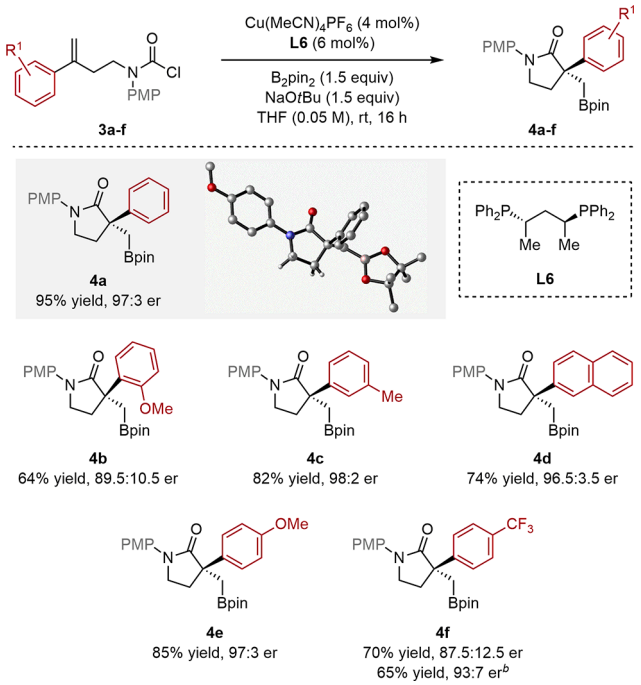
Scheme 3. Enantioselective 3,4-Disubstituted γ-Lactam Synthesis[a]



[a]Reactions performed on a 0.2 mmol scale; dr determined by ^{1}H NMR spectroscopic analysis of the crude. Isolated yields reported; er determined by chiral HPLC.

disubstituted γ-lactam (**4a**) (Scheme 4). More importantly, the chiral bisphosphine ligand **L6** gave **4a** in 95% yield and 97:3 er.

Scheme 4. Asymmetric Borylacylation of 1,1-Disubstituted Alkenes[a]

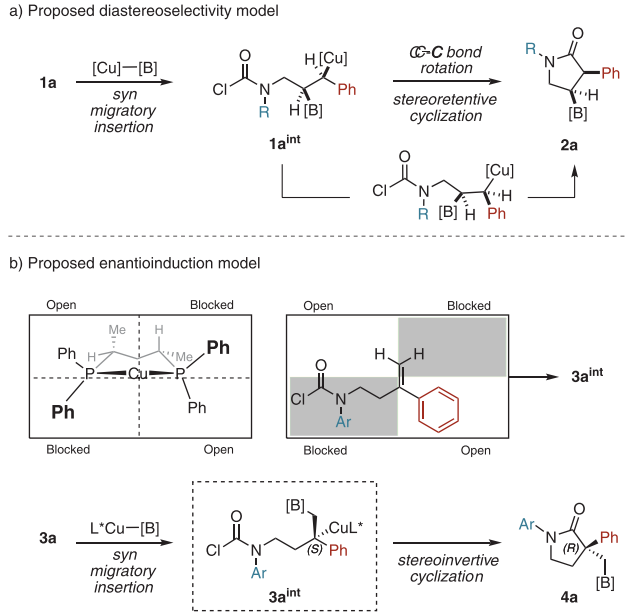


[a]Reactions performed on a 0.2 mmol scale. All reported yields are after isolation; er determined by chiral HPLC. [b]Reaction run using MTBE instead of THF.

Single crystal X-ray diffraction of **4a** was used to determine the absolute stereochemistry, and the stereochemistry of all other products was assumed by analogy. We surveyed the effect of aryl substituents on the styrenyl moiety. A bulky methoxy substituent at the *ortho* position of **3b** appeared to compromise the cyclization and delivered the product **4b** in moderate yield and enantioselectivity (64% yield, 89.5:10.5 er) In contrast, a substituent at the *meta* position gave **4c** in 82% yield and 98:2 er. A naphthyl substituent delivered product **4d** in excellent enantioselectivity (96.5:3.5 er) and good yield (74%). Likewise, an electron-rich substituent at the *para* position was tolerated, furnishing **4e** in 85% yield and 97:3 er. An electron-withdrawing group at this position resulted in an erosion in the enantioselectivity, as seen in product **4f**. We found that changing the solvent from THF to Et_2O improved enantioselectivity and delivered **4f** in 93:7 er and 65% yield.

On the basis of our results and previous literature,[18,19] we propose that a *syn* migratory insertion and stereoretentive cyclization leads to the observed *syn* stereoisomer of the 3,4-disubstituted γ-lactams (Scheme 5a). To investigate the origin

Scheme 5. Proposed Diastereo- and Enantioselectivity Models



of enantioinduction of the 3,3-disusbtituted products, we generated a quadrant diagram to predict the enantiomer of the migratory insertion step (Scheme 5b). In our analysis, we propose the enantioselective borylcupration of styrene **3a** generates the benzylcopper intermediate **3a**^{int} with an *S*-configuration.[16] The subsequent cyclization of the benzylic copper species proceeds with stereoinversion to generate product **4a**, aligning with previous reports[16,18,20]

With the ability to increase the scale of the reaction, while maintaining yield and selectivity, we carried out the reaction of **1a** on a 2 g scale under reduced catalyst loading and increased concentration (Scheme 6a). The product was isolated in >20:1 dr and 75% yield. We then briefly examined reactions of the carbon−boron bond, including oxidation, to obtain product **5a** in 90% yield, with no deterioration of the diastereoselectivity (Scheme 6b). The boronate was also converted to a new carbon−carbon bond through a vinylation procedure, which delivered **5b** in 49% yield and >20:1 dr. In addition, a heterocycle could be installed at the β-carbon through a stereoretentive arylation procedure[21] to furnish product **5c** in synthetically useful yields while maintaining high diastereoselectivity.

In conclusion, we have developed a general and mild method to synthesize polyfunctionalized γ-lactams in a highly stereoselective manner. This strategy utilizes simple 1,2-disubstituted olefins in a facile intramolecular borylacylation to generate chiral 3,4-disubsituted γ-lactams in excellent diasteroselectivity. Furthermore, 1,1-disubstituted olefins can be employed to generate 3,3-disubstituted γ-lactams in excellent enantioselectivity. We demonstrated scalability of this methodology and reactivity of the boronate handle

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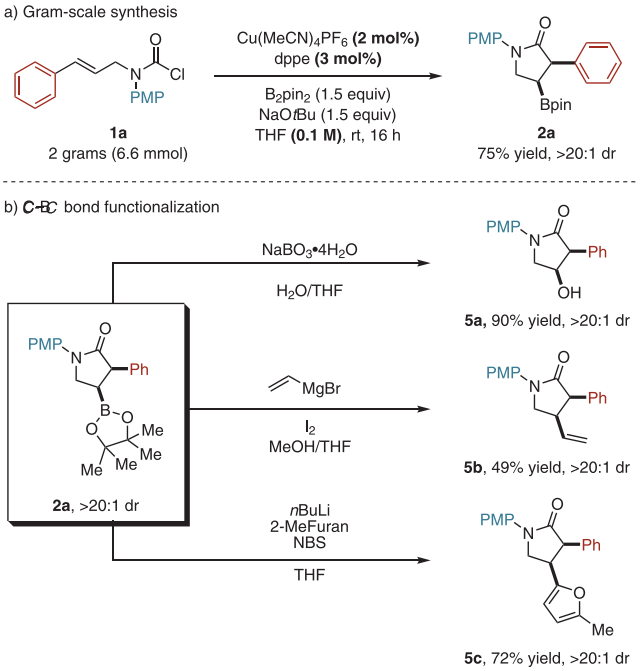
Scheme 6. Gram-Scale and Derivatizations[a]



[a]All reported yields are after isolation. dr determined by ^{1}H NMR spectroscopic analysis of the crude. PMP = *para*-methoxyphenyl. See the Supporting Information for details.

through various derivatizations of the γ-lactam scaffold. This methodology offers a route to the highly sought-after γ-lactams through copper-catalyzed borylative difunctionalizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02837.

Experimental procedures, characterization data, crystallographic data for **2a** and **4a**, NMR spectra, and HPLC spectra for new compounds (PDF)

Accession Codes

CCDC 2023481−2023482 contain 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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