Kinetic Resolution

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Regioselective Hydroarylations and Parallel Kinetic Resolution of Vince Lactam**

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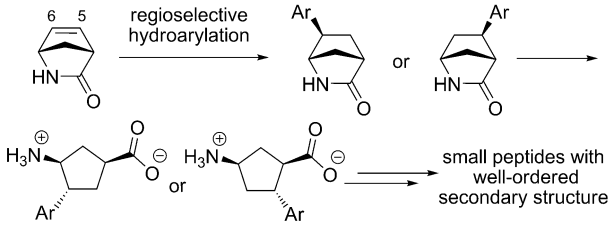
Modular small-molecule motifs that induce or mimic loop and turn secondary structure are important for the design of peptide-based drugs.[1] Incorporation of nonnatural structures into otherwise natural peptides can lead to favorable pharmacokinetic properties, such as increased cell permeability and oral bioavailability,[2] and is a prominent feature of successful pharmaceuticals, such as telaprevir[3] and boceprevir.[4] In the field of peptidomimetics and foldamers, oligomers containing γ-amino acids can form stabilized secondary structures,[5] can be resistant to serum and tissue proteases,[6] and can bind to biological macromolecules.[7] A γ-amino acid that has practical applications is γ-aminocyclopentanecarboxylic acid. This amino acid, which can be thought of as a γ-aminobutanoic acid (GABA) mimic locked in a W conformation, has been used in small peptides to reveal secondary structure sheets[8] and turns.[9] Access to such constrained residues with a limited range of accessible conformations is important and can greatly influence the pharmacology and properties of designed peptides.[10] Additionally, in the field of nanomanufacturing, the motif has been integrated into peptide-based nanotubes.[11] As a result, constrained γ-amino acids are of much interest to the pharmaceutical industry, because they can augment the existing set of fragments used to probe secondary structure, tune biological activity, and alter physicochemical properties of peptides.

We sought access to diverse substituted γ-aminocyclopentanecarboxylic acids as modular building blocks in our drug discovery program. Substituted γ-aminocyclopentanecarboxylic acids have been synthesized previously, but the syntheses can be lengthy and nondivergent,[9] which would be impractical for the synthesis of libraries of compounds. One strategy for late diversification is the hydroarylation of Vince lactam (2-azabicyclo[2.2.1]hept-5-en-3-one) followed by ring opening (Scheme 1).[12] Vince lactam is commercially available and has been utilized as a versatile synthetic building block in biomimetics and therapeutics.[13] Hydroarylations of the Vince lactam double bond are typically nonselective or favor arylation at the 6-position.[14] In general, regioselective addition to unactivated, unsymmetrical cyclic olefins is challenging. Herein, we report methods for the regioselective hydroarylation of Vince lactam to afford either the 5- or 6-aryl-substituted bicyclic lactams. The results were then used as inspiration for a regiodivergent parallel kinetic resolution.



Scheme 1. Regioselective hydroarylation strategy toward a diverse set of substituted γ-aminocyclopentanecarboxylic acids.

The term parallel kinetic resolution was first used by Vedejs and Chen in 1997.[15] For this type of resolution, a racemic sample is subjected to reaction conditions that independently change each enantiomer into new products that are no longer enantiomeric (as opposed to traditional kinetic resolutions, in which one enantiomer is unchanged).[16] Although Vince lactam is commercially available in enantiomerically enriched form from bioenzymatic resolutions,[17] the racemic mixture is less expensive. Furthermore parallel kinetic resolutions[18] are underutilized owing to their oftentimes serendipitous discovery. We were able to predict and develop a parallel kinetic resolution of (±)-Vince lactam after observing that the regioselectivity of the hydroarylation reaction depended on the absolute configuration of the ligand (see below).

The Rh-catalyzed hydroarylation conditions developed by Lautens and co-workers[19] for the enantioselective desymmetrization of diazabicycles were applied to and optimized for the regioselective reactions of enantiopure lactam presented here. We quickly discovered that in wet, nitrogen-sparged THF, one of the most common Josiphos ligands (**L1**) with a Rh^{I} complex efficiently facilitated the coupling of phenyl boronic acid to (+)-Vince lactam with high selectivity for the 6-position (Table 1, entry 1). The regiochemistry was confirmed by X-ray crystallography. Only the *exo* product was observed.

The mild and operationally simple conditions could be extended to numerous aryl boronic acids (Table 1). The electronic nature of the arene had little effect on the reaction as electron-rich and electron-poor arenes coupled efficiently. Additionally, *para*-, *meta*-, and *ortho*-substituted aryl boronic acids were suitable coupling substrates. Arenes containing protic functionality or aldehydes were not suitable. Nitrogen-

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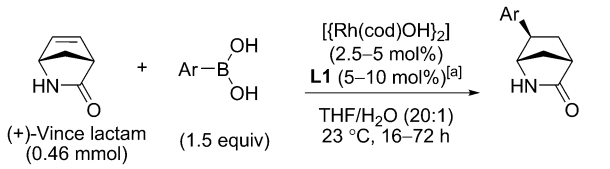
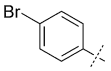
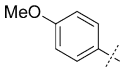
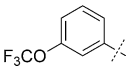
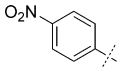
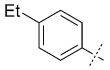
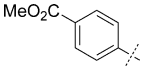
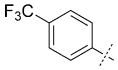
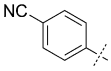
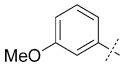
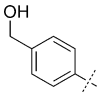
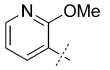
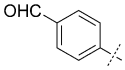
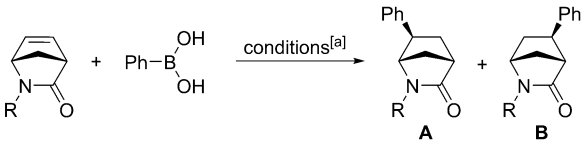
Table 1: Scope of regioselective hydroarylation.



Entry	Ar	Yield [%][b]	Entry	Ar	Yield [%][b]
1		76	8		83[c]
2		75	9		78
3		80	10		87
4		76	11		89[d]
5		83	12		76
6		86	13		0
7		82	14		0

[a] **L1** = (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine ((*R*,*S*)-*t*Bu-Josiphos). [b] Yield of isolated product after column chromatography. [c] 10 mol% of [{Rh(cod)OH}$_2$], 20 mol% of **L1**. [d] 77% yield of isolated product on gram scale. cod = cycloocta-1,5-diene.

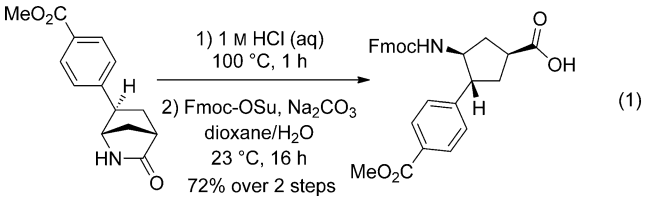
Table 2: Regioselectivity of hydroarylation dependent on ligand and nitrogen substitution.



Entry	R	Ligand	**A**/**B**[b]
1	H	**L1**	only **A**[c,d]
2	H	**L2**	only **A**[c]
3	H	*ent*-**L1**	1:2.5
4	H	*ent*-**L2**	1:1
5	Boc	*ent*-**L2**	SM[e]
6	Ts	*ent*-**L2**	SM[e]
7	Bn	*ent*-**L1**	1:7
8	Bn	*ent*-**L2**	1:3
9	PMB	*ent*-**L1**	1:7
10	3,4-DMB	*ent*-**L1**	1:6
11	DPM	*ent*-**L1**	1:5
12	2-NAP	*ent*-**L1**	1:7
13	Me	*ent*-**L1**	1:5
14	Ph	*ent*-**L1**	1:2

[a] Reaction conditions: enantiopure lactam (0.46 mmol), boronic acid (1.5 equiv), [{Rh(cod)OH}$_2$] (5 mol%), ligand (10 mol%), THF/H_2O (20:1; 6.3 mL), 23 °C, 16 h; analysis of the reaction mixtures showed complete consumption of lactam starting material. [b] Ratio of products, as determined by ^{1}H NMR spectroscopy. [c] Regioisomer not detected by ^{1}H NMR spectroscopy. [d] 76% yield of isolated product. [e] No product formation, starting material recovered. Boc = *tert*-butyloxycarbonyl, Bn = benzyl, 3,4-DMB = 3,4-dimethoxybenzyl, DPM = diphenylmethyl, **L2** = (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine ((*R*,*S*)-Josiphos), 2-NAP = 2-naphthyl, PMB = *para*-methoxybenzyl, Ts = *para*-toluenesulfonyl.

containing heteroaryl boronic acids can be coupled under these conditions, but only when coordination of the nitrogen atom to the metal center is disfavored. The reaction has been conducted on gram-scale without modification of the procedure and with comparable yield. For use in common peptide applications, arylated bicycles can be transformed into Fmoc-protected amino acids in two steps [Eq. (1); Fmoc–OSu = 9-fluorenylmethoxycarbonyl-*N*-hydroxysuccinimide].



(1)

Accessing the complementary regioisomeric substituted γ-aminocyclopentanecarboxylic acids proved more challenging. During initial optimization of the arylation, matched/mismatched pairing was observed between the absolute configuration of the substrate and ligand. It was discovered that use of the two enantiomers of either the **L1** or **L2** ligand could lead to surprisingly different selectivity outcomes (Table 2, entries 1 vs. 3 and 2 vs. 4). The use of one enantiomer gave exclusively the 6-substituted bicycle, whereas use of the other provided a mixture of the 5- and 6-substituted products, even slightly favoring the 5-substituted isomer. A survey of additional Josiphos-based ligands did not result in improved regioselectivity (results not shown) and alternative solutions were devised.

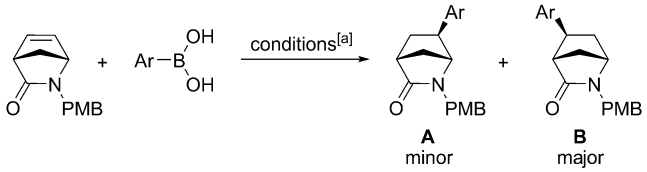
We hypothesized that the addition of a substituent on the nitrogen atom of the amide might alter the steric and the electronic environment of the double bond to favor arylation at the 5-position more strongly. Although certain *N*-substituted lactams (Boc, Ts; Table 2, entries 5 and 6) could not be arylated under the given reaction conditions, a marked improvement in selectivity was observed for *N*-alkylated lactams compared with the corresponding nonalkylated lactam.

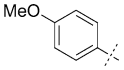
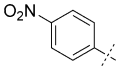
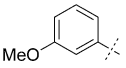
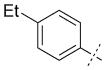
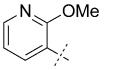
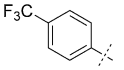
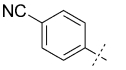
Hydroarylation of lactams with Bn and PMB groups led to the desired 5-arylated products in greater selectivity when the enantiomers of the ligands were used (Table 2, entries 7–9). Regiochemistry was confirmed again by X-ray crystallography and NMR studies. To better understand the role of alkylation and perhaps improve the regioselectivity further, lactams with benzyl derivatives that were more electron donating (Table 2, entry 10), larger (Table 2, entry 11), or had extended π systems (Table 2, entry 12) were synthesized, but use of these did not lead to improved product selectivity. Methylated lactam gave improved selectivity compared with the unsubstituted lactam (Table 2, entry 13), but the phenyl derivative did not (Table 2, entry 14). Taken together, the

results suggest that alkylation of the nitrogen atom may change the polarization of the olefin to begin to override the initially observed mismatch pairing.

To determine if this reversal of selectivity was general for other aryl groups, a variety of arylboronic acids were coupled to PMB-substituted Vince lactam (Table 3).[20] The regioselectivity was as good as, and oftentimes much better than, that with phenylboronic acid. Electron-poor arenes provided higher selectivity and *ortho*-substituted aryl boronic acids gave 5-substituted bicycles without any of the other isomer, as observed by ^{1}H NMR spectroscopy, completely reversing the regioselectivity compared to Table 1. Although some electron-rich and electron-neutral arenes provided the least isomerically enriched product mixtures, the selectivity was still sufficiently useful to obtain high yields of desired product, because the regioisomers were easily separable by column chromatography. Removal of the PMB group and ring opening to provide the amino acid could be accomplished in one reaction step by using trifluoroacetic acid [Eq. (2)].

Table 3: Scope of complementary regioselective hydroarylation.

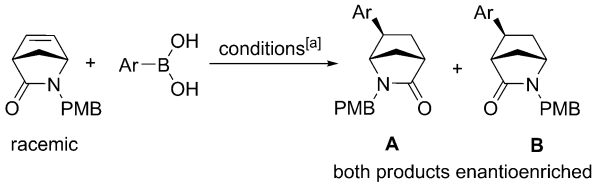


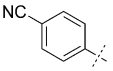
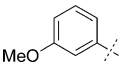
Entry	Ar	Yield **B** [%][b] (**A**/**B**)[c]	Entry	Ar	Yield **B** [%][b] (**A**/**B**)[c]
1		68[d] (1:7)	6		70 (1:7)
2		74 (1:6)	7		77[e]
3		81 (1:33)	8		71 (1:7)
4		73 (1:6)	9		70[e]
5		81 (1:13)	10		76 (1:27)

[a] See Table 1 for reaction conditions. [b] Yield of the isolated product after column chromatography. [c] Ratio of products, as determined by ^{1}H NMR spectroscopy. [d] Conducted on gram scale. [e] Only **B** was isolated. Regioisomer not detected by ^{1}H NMR spectroscopy.

Having established two successful and complementary regioselective arylations and given the exploratory results in Table 2, we postulated that a resolution of racemic Vince lactam might be possible, specifically a regiodivergent parallel kinetic resolution. To have both products isolated with high enantiomeric enrichment, we needed one set of reaction conditions under which each enantiomer of starting material would react with approximately equal and high selectively. The PMB-derivatized lactam was chosen to study this parallel kinetic resolution because the parent unsubstituted lactam would only provide one product with high enantiomeric enrichment. Four arbitrarily chosen arylboronic acids from previous experiments were individually coupled to a racemic sample of lactam in the presence of one enantiomer of the phosphine ligand and the Rh^I complex (Table 4). Eight aryl-substituted bicycles (two from each experiment) were isolated by column chromatography. The total yield of the isolated products was comparable to previous experiments, and was roughly split evenly between the two regioisomers. Enantiomeric enrichment of each isomer was good to excellent, as determined by enantiodiscriminating HPLC analysis. Notably, the products derived from *ortho*-tolylboronic acid had 97% and 99% *ee* (Table 4, entry 2), thus demonstrating a highly effective parallel kinetic resolution.

Table 4: Regiodivergent parallel kinetic resolution.

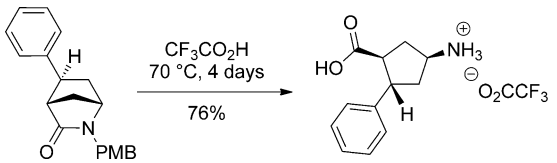


Entry	Ar	**A** Yield [%] (*ee*)	**B** Yield [%] (*ee*)
1		36 (76)	33 (90)
2		45 (99)	39 (97)
3		38 (89)	38 (96)
4		45 (78)	43 (91)

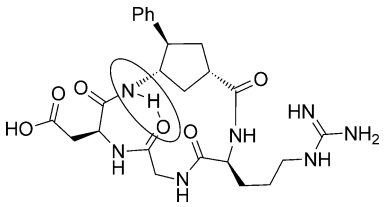
[a] See Table 1 for reaction conditions. Yield of isolated individual constitutional isomers after column chromatography given. Enantiomeric excess determined by enantiodiscriminating HPLC.

As a preliminary demonstration of their utility, we incorporated one of the constrained amino acids into a cyclic peptide by using standard solid-phase peptide synthesis. The small peptide is an analogue of peptides that contain the RGD sequence recognized by $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrin receptors.[21] NMR studies on the cyclic peptide[22] show that the residue participates in a reverse γ-turn, as predicted by previous γ-aminocyclopentanecarboxylic acid research (Scheme 2).[9]

The design of small peptides with enhanced properties benefits from small molecular motifs, such as conformationally constrained amino acids that impart organized and predictable secondary structure. We have developed conditions to regioselectively synthesize aryl-substituted γ-aminocyclopentanecarboxylic acids by the regioselective arylation



(2)



Scheme 2. Cyclic peptide containing γ-aminocyclopentanecarboxylic acid with reverse γ-turn hydrogen bond circled, as observed by NMR spectroscopy.

of either olefin carbon atom of Vince lactam. Additionally, we used the general conditions to develop a regiodivergent parallel kinetic resolution, which can provide two regioisomers, both in high enantiomeric excess from racemic starting material. The reaction products can be transformed into Fmoc-protected amino acids and incorporated into small peptides for drug discovery and molecular design applications.

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Keywords: arylation · kinetic resolution · regioselectivity · rhodium · Vince lactam

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