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Asymmetric Azidation−Cycloaddition with Open-Chain Peptide-Based Catalysts. A Sequential Enantioselective Route to Triazoles

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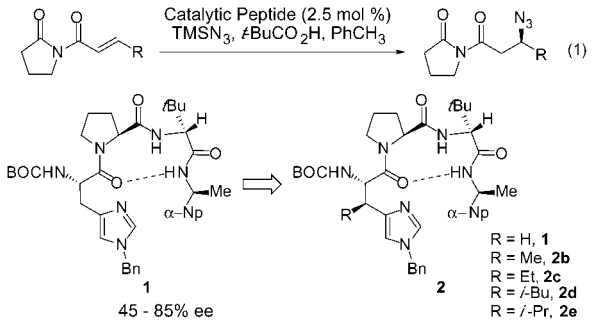
Recent advances in both the peptide design field and the area of high throughput catalyst screening have led to the discovery of small molecule, peptide-based organocatalysts that enable new enantioselective processes.[1] In this context, we recently disclosed a class of peptides that catalyze the conjugate addition of azide ion to α,β-unsaturated carbonyl compounds with moderate enantioselectivity (45−85% ee, eq 1).[2−4] The optimal catalyst (**1**) was found to adopt

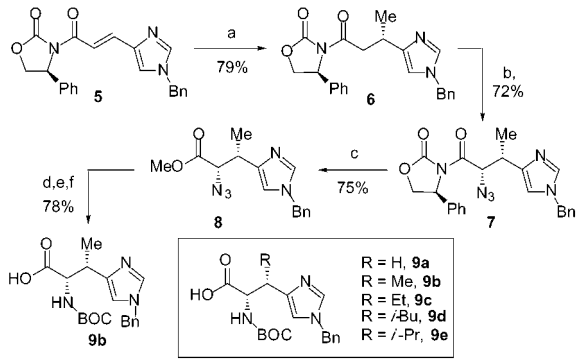


a β-turn-type structure, presumably favored by a L-Pro-D-*tert*-Leu sequence.[5] In addition, an amine base (e.g., the imidazole found in *N*-alkyl-His residues) proved to be essential for catalyst activity.[6] In searching for ways to improve catalyst enantioselectivity, we were drawn to the strategy of conformational rigidification through dihedral angle restriction.[7,8] We therefore targeted β-substituted His derivatives (e.g., **2**) as catalyst candidates that could provide selectivity and reactivity enhancement.[9] Reported herein are improved peptide-based azidation catalysts that take advantage of this design element. Their application to the synthesis of optically enriched triazoles and triazolines employing an azidation/cycloaddition sequence is also reported.[10]

The synthesis of the required β-substituted His residues was accomplished in analogy to reports by Hruby (Scheme 1).[11] Urocanic acid derivative **5** was subjected to diastereoselective conjugate addition employing MeMgBr in the presence of CuBr to afford derivative **6** (4:1 dr).[12] Asymmetric azidation according to the Evans procedure proceeded with complete diastereocontrol to afford α-azido imide **7** (72%).[13] Conversion to the *N*-BOC-protected amino acid was accomplished by employing a four-step sequence to give **9b** (59%). Analogous procedures were employed to afford **9c**−**e**, with other substituents in the β-position of the His derivative. Conversion of the β-substituted His derivatives to the derived azidation catalysts (**1**, **2b**−**e**, ***epi*-2c**) followed standard solution phase peptide synthesis procedures.[14]

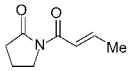
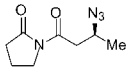
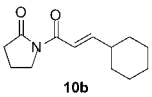
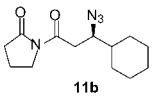
Presented in Table 1 are the results of enantioselective conjugate additions of azide with these catalysts. Entries 1 and 7 show the results with the previously reported unsubstituted catalyst **1**. Moderate enantioselectivity was observed with crotonate derivative **10a** (63% ee, 97% conversion); improved selectivity was observed

Scheme 1 [a]



[a] Conditions: (a) CH_3MgBr, CuBrDMS, THF, −40 °C, (b) KHMDS, THF, −50 °C; then trisyl azide, −78 °C; (c) NaOMe, $MeOH/CH_2Cl_2$, −10 °C; (d) H_2, Pd/C, AcOH/MeOH; (e) BOC_2O, CH_2Cl_2; (f) LiOH, THF/$MeOH/H_2O$.

Table 1. Catalyst Screen for β-azidation Employing Peptide Catalysts (**2**)[a]

Entry	Substrate	Product	Catalyst	Conv.[b]	ee[c]
1			**1**	97	63
2			**2b**	95	78
3			**2c**	100	76
4			**2d**	97	64
5	**10a**	**11a**	**2e**	83	47
6			***epi*-2c**	95	45
7			**1**	97	85
8			**2b**	95	89
9			**2c**	100	86
10			**2d**	97	77
11	**10b**	**11b**	**2e**	83	70
12			***epi*-2c**	74	68

[a] All reactions conducted at 25 °C. See Supporting Information for details. [b] Determined by ^1H NMR (400 MHz). [c] Determined by chiral HPLC. Reported ee values are the average of two runs. See Supporting Information for details.

with cyclohexyl-substituted acrylate **10b**, with **11b** being formed with 85% ee. Notably, the β-substituted catalysts afforded products with altered enantioselectivity under the same conditions (2.5 mol % **2**, 25 °C). In particular, methyl-bearing catalyst **2b** afforded improved ee values with both substrates. In the crotonate case, the product was obtained with 78% ee (entry 2), and for the cyclohexyl-substituted case, **11b** was formed with 89% ee (entry 8). Catalysts **2c**−**e** also afforded different levels of selectivity, supporting the notion that the β-stereogenic center substantively influences the transition state structures. For example, ethyl bearing catalyst **2c** led to the production of product **11a** with 76% ee (entry 3); isobutyl-substituted catalyst **2d** afforded the same product with 64% ee (entry 4); isopropyl catalyst **2e** afforded **11a** with only 47% ee (entry 5). The cyclohexyl-substituted acrylate provided a similar selectivity

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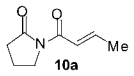
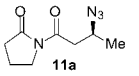
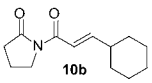
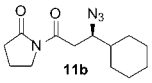
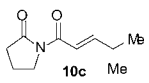
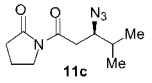
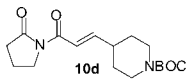
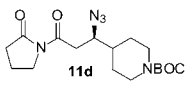
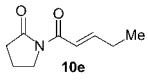
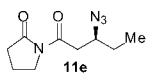
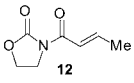
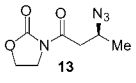
Table 2. Substrate Scope for β-Azidation Employing Peptide Catalysts (**1** and **2b**)[a]

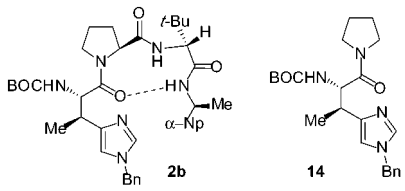
Entry	Substrate	Product	Temp (Catalyst)	Yield[b]	ee[c]
1	 **10a**	 **11a**	25 °C (**2b**)	90	78
2			-10 °C (**2b**)	90	86
3			25 °C (**1**)	97	63
4	 **10b**	 **11b**	25 °C (**2b**)	88	89
5			-10 °C (**2b**)	65	92
6			25 °C (**1**)	79	85
7	 **10c**	 **11c**	25 °C (**2b**)	89	84
8			-10 °C (**2b**)	75	90
9			25 °C (**1**)	84	82
10	 **10d**	 **11d**	25 °C (**2b**)	95	80
11			-10 °C (**2b**)	79	87
12			25 °C (**1**)	85	71
13	 **10e**	 **11e**	25 °C (**2b**)	95	77
14			-10 °C (**2b**)	83	85
15			25 °C (**1**)	91	71
16	 **12**	 **13**	25 °C (**2b**)	82	71
17			-10 °C (**2b**)	44	78
18			25 °C (**1**)	85	45

[a] All reactions conducted according to the optimized conditions. See Supporting Information for details. [b] After silica gel chromatography. Runs at −10 °C are conversions (^{1}H NMR, 400 MHz). [c] Determined by chiral HPLC. Reported ee values are the average of two runs. See Supporting Information for details.

profile. With catalyst **2c**, **11b** was obtained with 86% ee (entry 9); catalyst **2d** and **2e** afforded the product with 77% ee and 70% ee, respectively (entries 10 and 11). Finally, the epimeric catalyst ***epi*-2c** was substantially less selective for both substrates relative to **2c**: azide **11a** was formed in only 45% ee under its influence (entry 6), while **11b** was obtained in 68% ee under the same conditions (entry 12). These results underscore the functional significance of the β-position of the His residue. In addition, they reveal that improved selectivities may be achieved with a methyl group in the appropriate stereochemical configuration (cf. **2c** and ***epi*-2c**). However, a subtle remote steric effect is also at play: groups of greater steric bulk than methyl result in catalysts that afford lower selectivity (cf. **2b** with **2c**−**e**).

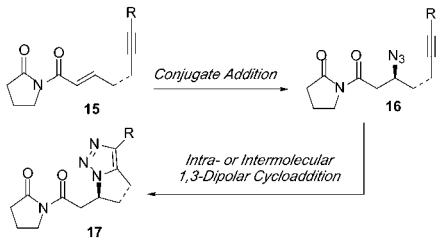
With catalysts of improved selectivity in hand, we sought to examine the scope of substrates that could undergo asymmetric azidation in the presence of catalyst **2b** (Table 2). Among the parameters that we examined was temperature. Thus, for substrate **10a**, enantioselectivity was enhanced with catalyst **2b** (entry 1, 78% ee; cf. 63% ee with **1**), and was further improved to 86% ee when the reaction was conducted at −10 °C (entry 2). Reactions are slower at the lower temperature; nevertheless, comparable levels of conversion can be achieved by carrying out the reaction for 48 h under these conditions (cf. 24 h at 25 °C). Whereas cyclohexyl-substituted substrate **10b** afforded **11b** with 89% ee at 25 °C (entry 4), the product was obtained in 92% ee at −10 °C (entry 5). Isopropyl-substituted acrylate **10c** gave similar results: azide **11c** was obtained with 84% ee at 25 °C (entry 7), and with 90% ee under the optimized conditions (entry 8). Piperdinyl-substituted compound **10d** afforded **11d** with 80% ee at 25 °C (entry 10; cf. 71% ee with catalyst **1**, entry 12), and 87% ee at the reduced temperature (entry 11). Similarly, the less sterically demanding acrylate **10e** was converted to azide **11e** with 77% ee at 25 °C (entry 13; cf. 71% ee with catalyst **1**, entry 15), but 85% ee at −10 °C. Finally, the more conventional oxazolidinone substrate **12** was converted to azide **13** with 71% ee at 25 °C (entry 16; cf. 45% ee with catalyst **1**, entry 18), and with 78% ee at −10 °C (entry 17). In general, these results represent improvements in enantioselectivity for these substrates relative to those obtained with catalyst **1**, unsubstituted at the β-position.[2]

The improvements in enantioselectivity are noteworthy in part because they are the result of substitution two carbons removed from the basic imidazole nitrogen in an open chain compound. Notably, catalyst **14** affords minimal enantioselectivity (<5% ee) for these conjugate additions, underscoring the importance of the secondary structure. An improvement in ee from 63% to 78% (i.e., the reactions of substrate **10a** with catalyst **1** versus **2b** at 25 °C, respectively) corresponds to a $\Delta(\Delta\Delta G^{\ddagger}) = 0.4$ kcal/mol of transition state energy differentiation. This quantity is clearly in the range that could be due to subtle changes in conformational equilibria. It is noteworthy that catalysts **1** and **2b**−**e** afford ^{1}H NMR spectra that are consistent with this possibility. For example, the benzylic protons within these catalysts exhibit chemical shift differences ($\Delta\delta$) that imply increasingly restricted rotation in that region:[15] **1**, $\Delta\delta$ = 0.08 ppm; **2b**, $\Delta\delta$ = 0.10 ppm; **2c**, $\Delta\delta$ = 0.20 ppm; **2d**, $\Delta\delta$ = 0.20 ppm; **2e**, $\Delta\delta$ = 0.46 ppm. On the other hand, for catalyst ***epi*-2c**, one of the least selective for the azidation, $\Delta\delta$ = 0.00 ppm (singlet). These observations suggest that the β-substituted His-containing peptides may indeed be rigidified with respect to their unsubstituted counterparts.



Chiral alkyl azides represent versatile synthons in organic synthesis.[16] We therefore set out to couple the asymmetric azidation to a second transformation to increase the potential utility of the reaction. We therefore attempted a sequential conjugate addition/1,3-dipolar cycloaddition sequence involving a pendant alkyne to access enantiomerically enriched triazoles (Scheme 2).[17] Substrates

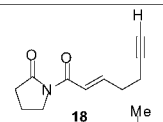
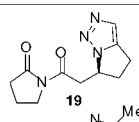
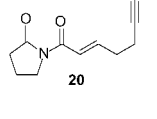
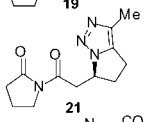
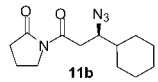
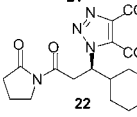
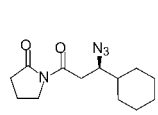
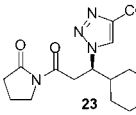
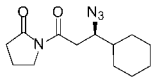
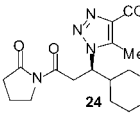
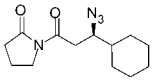
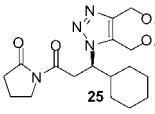
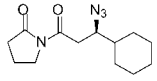
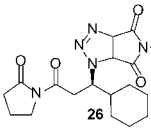
Scheme 2



of the type **15** were envisioned to undergo enantioselective azidation to produce intermediates **16**. Subsequent intra- or intermolecular cycloaddition was projected to produce the corresponding triazoles (**17**).

The synthesis of the key substrates was accomplished by standard methods. Asymmetric azidations were then carried out with improved peptide catalyst **2b** under the optimized conditions. The reaction mixtures were then filtered through silica plugs to remove the catalyst; concentration, followed by redissolving in toluene and heating (reflux or 130 °C; see Supporting Information for details) efficiently converted the azides to the corresponding triazoles. The results are summarized in Table 3. Noteworthy are that intramolecular and intermolecular cycloadditions proceed efficiently. Importantly, there was no erosion of substrate ee during the cycloaddition step. For example, acetylene-substituted substrate **18** undergoes conjugate addition to afford the derived azide with 82% ee. Filtration through a plug of silica gel, followed by heating to

Table 3. Enantioselective Azidation/Cycloaddition Sequence

Entry	Substrate	Product	Yield (%)[a]	ee (%)[b]
1	 **18**	 **19**	76	82[e]
2	 **20**	 **21**	83	86
3[c]	 **11b**	 **22**	73	92
4[c]		 **23**	85 (4:1)	92
5[c]		 **24**	78 (2:1)	92
6[c]		 **25**	77	92
7[d]		 **26**	79 (1:1)	92

[a] Combined yield for two steps after silica gel chromatography. Ratio in parentheses refers to ratio of regioisomers or diastereomers. [b] Determined by chiral HPLC. See Supporting Information for details. Enantioselectivities before and after the cycloaddition step were found to be ±2% ee. [c] Heated in the presence of the corresponding alkyne. See Supporting Information for details. [d] Heated in the presence of *N*-methylmaleimide. See Supporting Information for details. [e] The reported ee is for the azide precursor to **19**. The absence of ee erosion for this compound was inferred by analogy to entries 2−7, which were determined directly. See Supporting Information for details.

130 °C for 48 h then affords optically enriched triazole **19** in 76% overall (entry 1). Similarly, methyl-substituted substrate **20** is converted to triazole **21** in good overall yield and ee (86% ee, 83% isolated yield, entry 2). The sequence also works for cases where the asymmetric azidation is coupled to an intermolecular cycloaddition. For example, optically enriched azide **11b** (92% ee) can be converted by the same protocol to a number of cycloadducts with no erosion of ee. Cycloaddition with dimethylacetylenedicarboxylate yields triazole **22** in 73% yield (92% ee, entry 3). Use of methyl propiolate affords adduct **23** in 85% yield as a 4:1 mixture of regioisomers (92% ee, entry 4). Cycloaddition with ethyl butynoate yields adduct **24** in 78% overall yield as a 2:1 mixture of regioisomers, again with no loss of ee (entry 5). Condensation with bis(acetoxy)-2-butyne-diol produces triazole **25** in 77% overall yield (92% ee, entry 6). Finally, cycloaddition with *N*-methylmaleimide produces adduct **26** in 79% yield as a 1:1 mixture of diastereomers, but with no loss of enantioselectivity (entry 7).

The results presented herein indicate that introduction of substituents within open chain compounds can provide substantial improvement in catalyst selectivities. The perturbation of catalyst conformational equilibria with this approach could represent a general strategy for catalyst design, not only with small peptides but with other types of open chain catalysts as well. In the case of the asymmetric azidations reported herein, this improvement enabled the development of a two-step sequence for the production of optically enriched triazoles relying on 1,3-dipolar cycloadditions of the azidation products. Asymmetric transformations that set up further complexity-generating transformations have been shown to be of value in both target-oriented and diversity-oriented synthetic contexts. Studies along these lines are underway in our laboratory.

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Supporting Information Available: Experimental procedures and product characterization for all new compounds synthesized (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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