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COMMUNICATION

Catalytic Asymmetric Synthesis of 5-Membered Alicyclic α-Quaternary β-Amino Acids via [3+2]-Photocycloaddition of α-Substituted Acrylates

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The photocatalytically active salt of a cationic iridium polypyridyl complex and a chiral borate is competent to promote a highly stereoselective [3+2]-cycloaddition of cyclopropylurea with α-substituted acrylates. This protocol provides straightforward access to a variety of stereochemically defined 5-membered alicyclic α-quaternary β-amino acids, useful building blocks of β-peptides and peptidomimetics.

β-Amino acids, which are homologated variants of α-amino acids, constitute the basic structural components of β-peptides and peptidomimetics.[1,2] Chiral β-amino acid frameworks are frequently found in physiologically active compounds, including β-lactam antibiotics. Hence, greater attention has been paid to the utility of β-amino acids as intermediates toward more complex products than to their intrinsic pharmacological properties. Given this scenario, considerable efforts have been devoted to the development of synthetic methods to obtain acyclic and cyclic β-amino acids bearing substituents at various positions in a stereoselective manner.[3] Nevertheless, alicyclic β-amino acids, in which both the amino and carboxylic acid functionalities are vicinally attached to an aliphatic carbocycle, remain challenging targets due to the intrinsic difficulty associated with the simultaneous control of the absolute and relative stereochemistry of two adjacent stereocenters.[4] Among alicyclic β-amino acids, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (*cispentacin*) and its derivatives are particularly important because of their physiological characteristics such as strong antibacterial activity as well as conformational rigidity beneficial for regulating the secondary and tertiary structures of peptides. Accordingly, several reliable protocols have been developed for their preparation;[5] however, catalytic asymmetric methodologies are very limited, and none of the available systems are applicable for the simultaneous construction of the primary structure and stereochemical integrity of α-quaternary congeners.[6,7] Here, we describe our photocatalytic[8] approach to address this problem, thereby enabling a highly stereoselective assembly of 5-membered alicyclic α-quaternary β-amino acids and their derivatives.

Recently, we developed an efficient asymmetric [3+2]-cycloaddition of cyclopropylamine with α-substituted styrenes under visible-light irradiation[9] based on the use of urea as a redox-active anion-recognizable directing group and an iridium-chiral borate ion pair [*rac*-Ir][**1**] as a photocatalyst (Figure 1).[10] The key reactive intermediate in the stereoselective photocycloaddition is the cyclopropylurea-derived distonic radical cation, which acts as an electron-rich nucleophilic radical. We thus speculated that if α-substituted acrylates[11] could be employed as electron-deficient acceptors for the distonic radical cation, this catalytic system would serve as a powerful tool for the asymmetric synthesis of 5-membered alicyclic α-quaternary β-amino acids. As an initial attempt to examine this possibility, a mixture of cyclopropylurea **2** and methyl methacrylate (**3a**) in dichloromethane was exposed to the optimal conditions for the cycloaddition with α-alkyl styrenes (irradiation with a blue LED (470 nm) in the presence of [*rac*-Ir][**1a**] (5 mol%) at –30 °C for 12 h),[10] which indeed resulted in the formation of the desired cycloadduct, the protected β-amino acid ester **4a**, in 79% yield with a diastereomeric ratio (dr) of 6.4:1 (Table 1, entry 1). The enantiomeric excess of the major diastereomer was determined to be 91%. Fortunately, the stereochemical outcome was improved to a satisfactory level upon increasing the substrate concentration and reaction temperature, and **4a** was obtained in 83% yield (dr = 15:1) with 94% ee for the major diastereomer (entry 2). Subsequent experiments performed with catalysts having borate ions **1** of different structures[10,12] revealed that the *n*-butoxy groups on the geminal aromatic substituents (Ar) of the 1,3,2-oxazaborolidin-4-one moiety were imperative for attaining high stereoselectivity (entries 3 and 4). The presence

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of 2,4,6-triisopropylphenyl (TRIP) groups at the 6,6'-positions of the binaphthyl backbone also appeared to be crucial for the present stereocontrol (entry 5).

Figure 1 Structure of chiral iridium borate

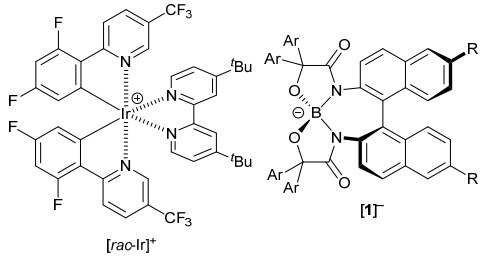
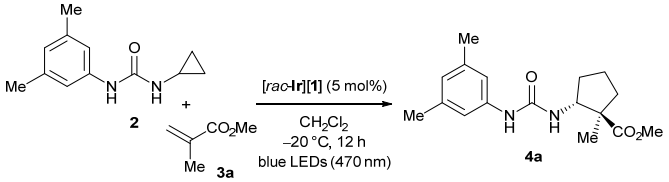


Table 1 Optimization of reaction conditions[a]

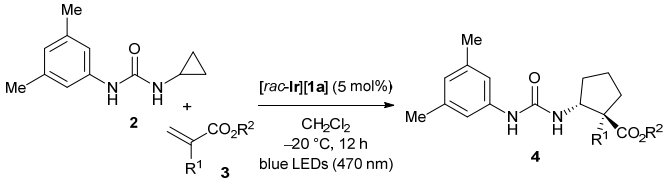


Entry	**1** (Ar, R)	Yield (%)[b]	dr[c]	ee (%)[d]
1[e]	**1a** (3,5-(^{n}BuO)$_2$C$_6$H$_3$, TRIP)	79	6.4:1	91
2	**1a**	83	15:1	94
3	**1b** (3,5-(^{n}Pent)$_2$C$_6$H$_3$, TRIP)	62	1.4:1	35/rac
4	**1c** (3,5-(MeO)$_2$C$_6$H$_3$, TRIP)	65	1.4:1	34/rac
5	**1d** (3,5-(^{n}BuO)$_2$C$_6$H$_3$, H)	81	5.6:1	56/rac

[a] Unless otherwise noted, the reaction was performed with **2** (0.1 mmol), **3a** (0.5 mmol), and [*rac*-Ir(dFCF$_3$ppy)$_2$(dtbbpy)][**1**] (5 mol%) in CH_2Cl_2 (0.2 M) for 12 h under blue LEDs (470 nm) irradiation at –20 °C. [b] Isolated yield was reported. [c] Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude aliquot. [d] Enantiomeric excess (ee) was determined by chiral HPLC analysis using DAICEL CHIRALCEL OZ-3. [e] Reaction was performed in 0.1 M CH_2Cl_2 solution at –30 °C. TRIP = 2,4,6-^{i}Pr$_3$C$_6$H$_2$

Under the optimised reaction conditions, the scope of this asymmetric photocycloaddition was explored with various α-substituted acrylates **3** (Table 2). The straight-chain alkyl substituent could be elongated without affecting the stereochemical outcome (entries 1-3), and an excellent selectivity profile was also observed with acrylates bearing 4-*tert*-butylbenzyl and isobutyl groups at the α-position (entries 4 and 5). Various functional groups such as terminal olefins, chlorine, ethers, and esters were well tolerated, and the corresponding cycloadducts **4** were obtained with rigorous enantiocontrol, although the degree of diastereocontrol varied to a certain extent (entries 6-10). An acrylate with a redox-active *N*-Boc-protected indole moiety underwent smooth cycloaddition under the present photoredox conditions to afford the desired product **4l** in high chemical yield with moderate diastereoselectivity and good enantioselectivity (entry 11). When methyl acrylate was used as a radical acceptor, slight erosion of the enantiomeric excess was inevitable, while a satisfactory level of diastereoselectivity was attained (entry 12). The ester substituent of **3** could also be variable, and the steric hindrance caused a slight decrease in enantioselectivity (entries 13 and 14). The absolute configuration of **4** was assigned by analogy to that of **4e**, which was determined to be 1*R*,2*R* by single-crystal X-ray diffraction analysis (Figure 2).

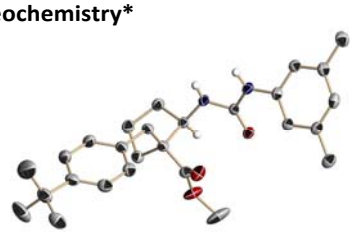
Table 2 Reaction scope[a]



Entry	R^1	R^2	**3**	yield (%)[b]	dr[c]	ee (%)[d]	**4**
1	$Me(CH_2)_3$	Me	**3b**	90	>20:1	96	**4b**
2	$Me(CH_2)_9$	Me	**3c**	92	>20:1	96	**4c**
3	$Ph(CH_2)_3$	Me	**3d**	95	>20:1	97	**4d**
4	4-^{t}BuC$_6$H$_4$CH$_2$	Me	**3e**	97	>20:1	95	**4e**
5	$(Me)_2CHCH_2$	Me	**3f**	92	>20:1	96	**4f**
6	CH_2=$CH(CH_2)_3$	Me	**3g**	81	18:1	97	**4g**
7	$Cl(CH_2)_3$	Me	**3h**	84	>20:1	97	**4h**
8	^{t}BuMe$_2$SiO$(CH_2)_3$	Me	**3i**	93	9.2:1	93	**4i**
9	$MeO(CH_2)_3$	Me	**3j**	84	13:1	94	**4j**
10	$PhCOO(CH_2)_3$	Me	**3k**	82	8:1	94	**4k**
11	(*N*-Boc-3-indolyl)CH_2	Me	**3l**	82	4:1	85	**4l**
12	H	Me	**3m**	85	11:1	85	**4m**
13	Me	^{t}Bu	**3n**	94	15:1	87	**4n**
14	Me	$PhCH_2$	**3o**	95	12:1	93	**4o**

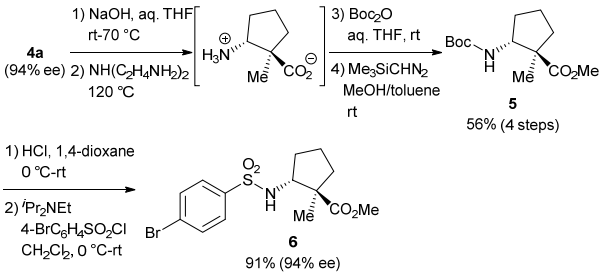
[a] The reaction was performed with **2** (0.1 mmol), **3** (0.5 mmol), and [*rac*-Ir(dFCF$_3$ppy)$_2$(dtbbpy)][**1a**] (5 mol%) in CH_2Cl_2 (0.2 M) for 12 h under blue LEDs (470 nm) irradiation at –20 °C. [b] Isolated yield was reported. [c] Dr was determined by ^{1}H NMR analysis of the crude aliquot. [d] Ee was determined by chiral HPLC analysis.

Figure 2 ORTEP diagram of 4e for determination of the absolute stereochemistry*



*The thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability level. Calculated hydrogen atoms except for those attached to the stereogenic carbon are omitted for clarity. Blue = nitrogen, red = oxygen, gray = carbon.

The cycloadducts could be readily converted into the corresponding *N*-Boc-protected β-amino esters, as exemplified in Scheme 1. The initial saponification of the ester moiety of **4a** with NaOH in aqueous THF, followed by treatment with triamine at 120 °C, generated a free β-amino acid.[13] Subsequent reactions with di-*tert*-butyl dicarbonate (Boc_2O) and trimethylsilyldiazomethane (Me_3SiCHN_2) were conducted sequentially at ambient temperature to isolate *N*-Boc methyl



Scheme 1 Deprotection

ester **5** in good yield. Conservation of the enantiomeric excess throughout these processes was confirmed by chiral HPLC analysis after conversion of **5** to **6** by replacing the Boc-protecting group with a 4-bromobenzenesulfonyl group.

In conclusion, we established a straightforward procedure for the asymmetric synthesis of 5-membered alicyclic α-quaternary β-amino acids, which relies on the chiral iridium borate-catalysed [3+2]-photocycloaddition of cyclopropylurea with α-substituted acrylates. This photocatalytic protocol was applicable to a range of acrylates bearing different α-substituents, and the corresponding cycloadducts were obtained with high diastereo- and enantioselectivities. Since the presence of cyclic structures and quaternary carbon atoms in amino acids is known to restrict the conformational flexibility of peptides, increasing the accessibility of stereochemically defined alicyclic β-amino acids would pave the way for the development of novel functional β-peptides and peptidomimetics.

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Conflicts of interest

There are no conflicts to declare.

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