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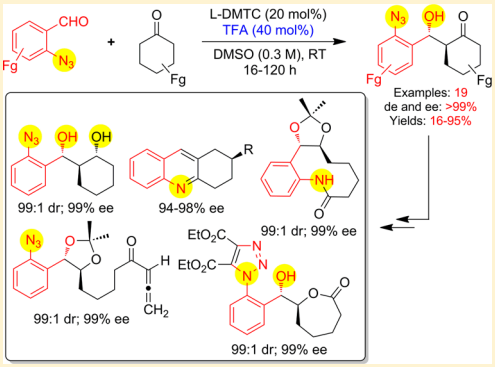
A Brønsted Acid-Amino Acid as a Synergistic Catalyst for Asymmetric List-Lerner-Barbas Aldol Reactions

Dhevalapally B. Ramachary* and Kodambahalli S. Shruthi

Catalysis Laboratory, School of Chemistry, University of Hyderabad, Central University (PO), Hyderabad 500 046, India

Supporting Information

ABSTRACT: Herein, for the first time, a combination of L-amino acid, (*R*)-5,5-dimethyl thiazolidinium-4-carboxylate (L-DMTC) with simple Brønsted acid TFA is reported as the suitable synergistic catalyst for the List-Lerner-Barbas aldol (LLB-A) reaction of less reactive 2-azidobenzaldehydes with various ketones at ambient temperature to furnish the optically active functionalized (2-azidophenyl)alcohols with very good yields, dr's, and ee's. This method gives first time access to the novel azido-containing multifunctional compounds, which are applicable in material to medicinal chemistry. Chiral functionalized (2-azidophenyl)alcohols were transformed into different molecular scaffolds in good yields with high selectivity through Lewis acid mediated $NaBH_4$ reduction, aza-Wittig and Staudinger reaction (azide reduction), followed by oxidative cyclizations, allenone synthesis, and click reaction, respectively. Chiral LLB-A products might become suitable starting materials for the total synthesis of natural products, ingredients, and inhibitors in medicinal chemistry. The mechanistic synergy of L-DMTC with TFA to increase the rate and selectivity of LLB-A reaction in DMSO-D_6 is explained with the controlled and online NMR experiments.

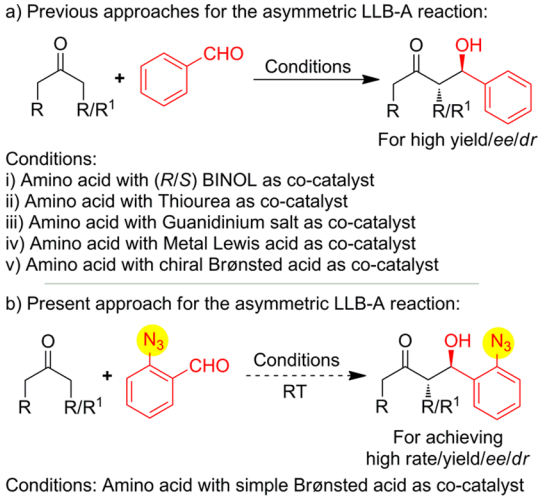


INTRODUCTION

In 2000, List, Lerner, and Barbas discovered the L-proline-catalyzed enamine-mediated asymmetric intermolecular aldol reaction, which has created a new realm in organic chemistry called as *organocatalysis*.[1] After this preliminary exploration, many chemists entered in this field to investigate the reaction scope by changing the catalysts along with co-catalysts and the different substrates of aldehydes and ketones.[2] In this connection, in order to increase the rate and selectivity of List-Lerner-Barbas aldol (LLB-A) reaction, (*S*)-BINOL,[3] Schreiner's thiourea,[4] TBD salt,[5] $ZnCl_2/CoCl_2$,[6] and chiral Brønsted acid, D-CSA[7], are used as promoters along with L-amino acid,[1,2] (*S*)-(−)-5-(2-pyrrolidinyl)-1*H*-tetrazole,[8] or Singh's prolinamide[9] as catalysts (Scheme 1a). Even though various combinations of catalysts/co-catalysts were used to achieve the best rate and selectivity for LLB-A reaction, at ambient conditions, so far it was not successful; either rate or selectivity is compromised (Scheme 1a).

In continuation of our recent interest in the development of supramolecular-organocatalysis and understanding the neighboring group participation in the *pre-* or *post*-transition state of organocatalytic reactions,[10] herein, we have chosen less reactive, functionalized 2-azidobenzaldehydes as the substrate with different ketones to study the enhancement in reaction rate and selectivity of LLB-A reaction under the catalysis of different L-amino acids along with known/unknown co-catalysts (Scheme 1b). Our main focus in this study is to develop the chiral polyfunctionalized products, which contain a medicinally/materialistically important *ortho*-azido group under simple ambient catalytic conditions.[11] For this design, we have chosen sterically and electronically challenging *ortho*-azidobenzaldehydes as the electrophile with cyclic/acyclic ketone as the pronucleophile with synergistic catalysis of L-amino acid and simple Brønsted acid (Scheme 1and Figure 1).

Scheme 1. Summary of Previous Work and the Design Plan of This Work



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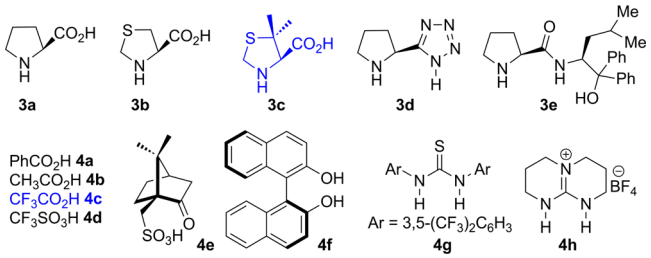


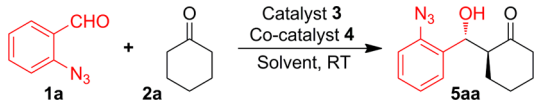
Figure 1. Library of catalysts and co-catalysts screened in this study.

RESULTS AND DISCUSSIONS

Synergistic Catalyst for Asymmetric List-Lerner-Barbas Aldol Reactions: Reaction Optimization. In the preliminary optimization, we have chosen LLB-A conditions of L-proline (**3a**) (20 mol %) as catalyst in DMSO for the reaction of *o*-azidobezaldehyde (**1a**) with cyclohexanone (**2a**) at room temperature for 24 h, which furnished the expected LLB-A product *anti*-(−)-**5aa** in only 16% yield with 91% ee in 4:1 dr (Table 1, entry 1). On obtaining very low yield, we further tested other amino acids such as L-thioproline (**3b**), (*R*)-5,5-dimethyl thiazolidinium-4-carboxylate (L-DMTC)[12] (**3c**), and (*S*)-(−)-5-(2-pyrrolidinyl)-1*H*-tetrazole[8] (**3d**) in DMSO at room temperature for 24−48 h, which also furnished low to good yields but with good ee and moderate dr (Table 1, entries 2−7). Among the tested amino acids, L-DMTC (**3c**)[12] gave promising results in terms of ee (99%) and dr (6:1) (Table 1, entry 3). The designed LLB-A reaction under the catalysis of Singh's prolinamide (**3e**)[9] with benzoic acid (**4a**) as the co-catalyst under neat conditions at −35 °C for 24 h furnished the *anti*-(−)-**5aa** in 91% yield with 98% ee and 99:1 dr (Table 1, entry 8). However, the same neat reaction at 25 °C for 2 h furnished the *anti*-(−)-**5aa** in 95% yield with decreased ee and dr (Table 1, entry 9). Even though the Singh's catalyst **3e** furnished good yield and selectivity, the reaction temperature was too low to be applicable universally, which is deviating from the main goal that we are on the lookout for reactions at ambient conditions. When we performed the reaction at room temperature, the results were not appreciable (Table 1, entry 9). In this regard, as mentioned earlier, since L-DMTC (**3c**) gave good selectivity but low yield/rate, we extended our investigations further to check whether the yield/rate of the reaction could be increased by using L-DMTC (pK_a = ∼9.76) (**3c**) in combination with Brønsted acid co-catalysts such as benzoic acid (pK_a = 11.1) (**4a**), acetic acid (pK_a = 12.3) (**4b**), trifluoroacetic acid (pK_a = 3.45) (**4c**), and trifluoromethanesulfonic acid (pK_a = 0.3) (**4d**) (Table 1, entries 10−14). Among these Brønsted acid co-catalysts, when used in pair with L-DMTC (**3c**) (20 mol %), trifluoroacetic acid (**4c**) (40 mol %) seems to be ideal in providing good yield/rate as well as excellent ee and dr (Table 1, entry 13). The same combination of catalysts **3c**/**4c** when used in a different solvent acetonitrile furnished a low yield with low selectivity, whereas, in DMSO-D_6, only the yield was reduced (Table 1, entries 15 and 16). Synergistic combination of **3c** (20 mol %) with 20 or 30 mol % of **4c** also in DMSO at 25 °C for 24 h furnished **5aa** with reduced yield (76−78%), but the selectivity remained unchanged (results not shown in Table 1). There is no LLB-A reaction observed even after 48 h at 25 °C under only TFA (**4c**)-catalysis in DMSO (not shown in Table 1).

After realizing the importance of the role played by TFA (pK_a = 3.45) (**4c**) in boosting the yield/rate, we were curious to know how well it works when used along with L-proline (**3a**) (pK_a = 12.3) and L-thioproline (pK_a = ∼9.33) (**3b**) (Table 1, entries 17 and 18) and disappointed to find that, even though there was an unsatisfactory increase in yield, there was also a noticeable drop in ee. In a similar manner, TFA (**4c**) with proline-tetrazole (pK_a = 11.26) **3d**-catalysis also gave disappointing results with decreased yield and slightly increased ee/dr (Table 1, entry 19). Switching back to L-DMTC (**3c**), we also wanted to check the contribution to yield and selectivity by a chiral Brønsted acid, D-CSA (pK_a = 5.61) (**4e**), as co-catalyst, but it furnished only poor yield with moderate selectivity (Table 1, entry 20). Simultaneously, we were interested in screening hydrogen-bond donating compounds such as (*S*)-BINOL (pK_a = 13.22) (**4f**), Schreiner's thiourea (pK_a = 8.5) (**4g**), and TBD salt (pK_a = 25.98) (**4h**) as the co-catalysts along with L-proline (pK_a = 12.3) (**3a**), as they were recently reported in the literature to be better co-catalysts when used in combination with amino acids. Utilization of Schreiner's thiourea (**4g**) as co-catalyst in hexane solvent provided only moderate yield with excellent ee and dr, whereas (*S*)-BINOL (**4f**) furnished moderate yield and excellent dr but with little lower ee, while TBD salt (**4h**) under neat reaction conditions resulted in comparable yield and ee with the catalyst **3c**/**4c**

Table 1. Reaction Optimization[a]



entry	catalyst **3**	co-cat. **4**	solvent	*t* (h)	yield (%)[b] **5aa**	ee (%)[c]	dr[d]
1	**3a**	-	DMSO	24	16	91	4:1
2	**3b**	-	DMSO	24	16	98	8:1
3	**3c**	-	DMSO	48	25	99	6:1
4	**3c**	-	NMP	48	15	98	6:1
5	**3c**	-	CH_3CN	48	17	90	6:1
6	**3c**	-	Neat	48	20	92	6:1
7	**3d**	-	DMSO	24	90	91(96)	1:2
8[e]	**3e**	**4a**	Neat	24	91	98	99:1
9	**3e**	**4a**	Neat	2	95	83	5:1
10	**3c**	**4a**	DMSO	48	28	96	6:1
11	**3c**	**4a**	CH_3CN	96	16	79	6:1
12	**3c**	**4b**	DMSO	24	20	96	6:1
13	**3c**	**4c**	**DMSO**	**24**	**88**	**99**	**17:1**
14	**3c**	**4d**	DMSO	24	16	67	18:1
15	**3c**	**4c**	CH_3CN	24	47	92	17:1
16	**3c**	**4c**	DMSO-D_6	24	74	99	17:1
17	**3a**	**4c**	DMSO	24	29	80	7:1
18	**3b**	**4c**	DMSO	24	58	91	18:1
19	**3d**	**4c**	DMSO	24	88	95(82)	3.5:1
20	**3c**	**4e**	DMSO	48	13	85	30:1
21[f]	**3a**	**4g**	Hexane	24	53	>99	99:1
22[g,h]	**3a**	**4f**	DMSO	24	72	97	99:1
23[g]	**3a**	**4f**	DMSO	10	76	95	99:1
24[i,h]	**3a**	**4h**	Neat	24	60	>99	8:1
25[i]	**3a**	**4h**	**Neat**	**24**	**88**	**99**	**7.7:1**

[a]Unless otherwise mentioned, all reactions were carried out with **1a** (0.3 mmol), cyclohexanone **2a** (4.2 mmol, 14 equiv), catalysts **3** (20 mol %) and **4** (40 mol %) in DMSO (0.3 M) at RT. [b]Yield refers to the column-purified product of both the isomers. [c]ee was determined by CSP-HPLC analysis, and parentheses values refer to the *syn*-isomer. [d]dr was determined based on ^{1}H NMR analysis of crude compound or HPLC analysis. [e]Reaction was carried out using **3e** (10 mol %) and **4a** (10 mol %) under neat conditions at −35 °C. [f]**3a** and **4g** (each 10 mol %) were used in hexane (0.14 M). [g]**3a** (30 mol %) and **4f** (1 mol %) were used in DMSO (1.25 M). [h]Reaction was carried out at 0 °C. [i]**3a** (15 mol %) and **4h** (10 mol %) were used under neat conditions at RT.

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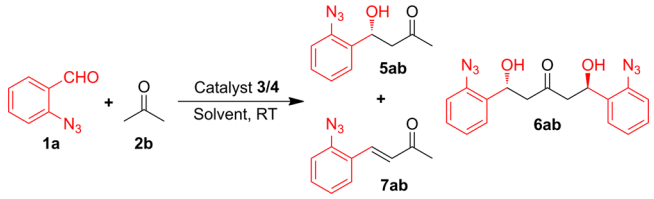
Table 2. Reaction Optimization[a]



entry	catalyst 3	co-cat. 4	solvent	t (h)	yield (%)[b] 5ab	ee (%)[c] 5ab	yield (%)[b] 7ab	yield (%)[b,d] 6ab	ee (%)[c] 6ab
1[e]	3c	4c	DMSO	24	21	85	21		
2[f]	3a	4h	neat	24	57	64	20		
3[g]	3e	4a	neat	4	79	59			
4[h]	3e		neat	5	85	70		<3	
5[g,i]	3e	4a	neat	24	29	61		21	>99
6[h,i]	3e		neat	24	32	79		23	98
7	3a		DMSO	3	88	72	12		
8	3a		DMF	6	64	66	14		
9	3a		NMP	6	88	73	7		
10	3c		DMSO	12	65	87	6		
11[j]	3c		NMP	24	12	88			
12	3c		CH_3CN	9	69	86	3		
13	3d		DMSO	3	86	73	12		

[a]Unless otherwise mentioned, all reactions were carried out with **1a** (0.3 mmol), acetone **2b** (1.5 mmol, 14 equiv), catalysts **3** (20 mol %) in DMSO (0.25 M) at RT. [b]Yield refers to the column-purified product. [c]ee was determined by CSP-HPLC analysis. [d]dr was determined based on ^{1}H NMR or HPLC analysis. [e]**3c** (20 mol %) and **4c** (40 mol %) were used. [f]**3a** (15 mol %) and **4h** (10 mol %) were used. [g]**3e** (10 mol %) and **4a** (10 mol %) were used. [h]**3e** (10 mol %) was used. [i]Reaction was carried out at −35 °C. [j]Reaction was carried out at 4 °C.

system but with lesser dr (Table 1, entries 21−25). Finally, the best optimized reaction conditions were found to be the combination of catalysts **3c** (20 mol %) and **4c** (40 mol %) in DMSO at room temperature. The acidity of the Brønsted acid co-catalysts, structure of the amino acid, and solvent nature seem to be playing an essential role in controlling the rate and selectivity, which will be discussed elaborately in the mechanistic section.

After completing the optimization studies and arriving at the above said best optimization conditions for the cyclohexanone, we shifted our attention onto the acyclic ketone acetone (**2b**). The LLB-A reaction on acetone (**2b**) using the best optimization conditions of **3c**/**4c** (Table 1 entry13) revealed that the expected aldol product (+)-**5ab** was obtained only in 21% yield and 85% ee, along with 21% of the elimination product **7ab** (Table 2, entry 1). The reason behind the formation of the elimination product **7ab** might be due to the acidity of the Brønsted acid co-catalyst **4c**. Even the second best optimized conditions, namely, **3a** with **4h** under neat reaction conditions, furnished the aldol product (+)-**5ab** in moderate yield and ee along with the elimination product **7ab** (Table 2, entry 2).

The catalyst system **3e**/**4a** under neat reaction conditions at room temperature generated the aldol product (+)-**5ab** in good yield but with moderate ee (Table 2, entry 3). The same reaction even in the absence of **4a** also furnished the product in more or less the same yield with a slight increase in ee, along with a negligible amount of the bis-aldol product **6ab** (Table 2, entry 4).[13] The very same reaction at low temperature using the catalyst **3e** in either the absence or the presence of **4a** produced the aldol product in low yield with moderate ee, but with increased yield of the bis-aldol product (+)-**6ab** with 98−99% ee (Table 2, entries 5 and 6). With these unsatisfactory results for the acetone under the combination catalyst system, we shifted our focus back to the conventional usage of just the amino acids instead. The aldol reaction of acetone (**2b**) with *o*-azidobenzaldehyde (**1a**) under L-proline (**3a**) catalysis in DMSO, furnished the product in 88% yield with 72% ee (Table 2, entry 7). The results were almost the same even in the other two solvents DMF and NMP (Table 2, entries 8 and 9). Under L-DMTC (**3c**) catalysis in DMSO solvent, the product was obtained in 65% yield with 87% ee and also the results were comparable in acetonitrile solvent, whereas the same catalyst in NMP as solvent furnished the product in poor yield but with the same ee (Table 2, entries 10−12). L-Proline based tetrazole (**3d**) also catalyzed the reaction in a similar manner (Table 2, entry 13). At the end, it is obvious from Table 2, that L-DMTC (**3c**) catalysis in DMSO solvent is the best optimized condition for the acetone.

Asymmetric Synthesis of LLB-A Products 5ba−ia. After testing the applicability of the LLB-A reaction on the acyclic ketone, acetone (**2b**), we focused our attention to study the scope of the reaction, utilizing various functionalized *o*-azidobenzaldehydes. Initially, the reaction was carried out on halo-substituted *o*-azidobenzaldehydes **1b−1e** with cyclohexanone (**2a**) using the best optimized catalyst **3c**/**4c** system to furnish the products *anti*-(−)-**5ba−5ea** in very good yields with good dr and excellent ee (Table 3, entries 1−4). The LLB-A reaction of 2,4-diazidobenzaldehyde (**1f**) with **2a** resulted in the product *anti*-(−)-**5fa** with less yield but with increased dr and 98% ee (Table 3, entry 5). *o*-Azidobenzaldehydes possessing an electron-withdrawing group such as *p*-(trifluoromethyl) and *p*-cyano groups **1g** and **1h** also underwent the reaction to provide the products *anti*-(+)-**5ga** and *anti*-(−)-**5ha** in good yields with good dr and excellent ee (Table 3, entries 6 and 7). The presence of an electron-donating substituent like the dioxymethylene group on *o*-azidobenzaldehyde, **1i**, also did not deter the reaction, but produced the product *anti*-(−)-**5ia** in somewhat lesser yield but with good dr and 97% ee (Table 3, entry 8). In this particular exercise, wherever we observed

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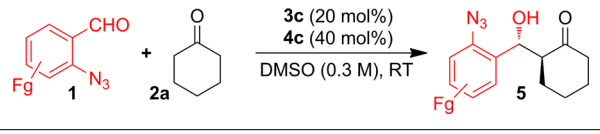
Table 3. Scope of the L-DMTC (3c) and TFA (4c) Catalyzed LLB-A Reactions[a]



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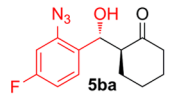
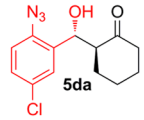
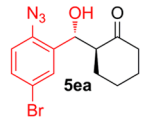
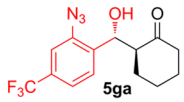
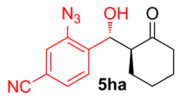
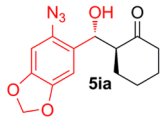
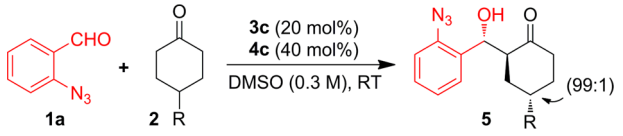
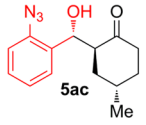
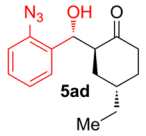
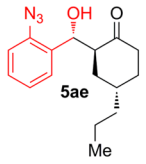
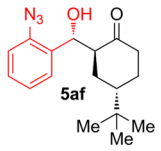
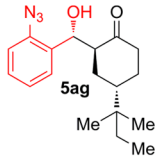
1	 5ba	24	75	17:1	99
		24[f]	91	17:1	>99
2	 5ca	36	89	17:1	98
3	 5da	18	90	51:1	99
4	 5ea	24	79	17:1	>99
5	 5fa	48	41	99:1	98
		36[f]	93	13:1	99
6	 5ga	16	85	17:1	>99
7	 5ha	18	90	21:1	>99
8	 5ia	120	46	17:1	97
		120[f]	51	2.4:1	99

[a]Unless otherwise mentioned, all reactions were carried out with **1** (0.3 mmol), cyclohexanone **2a** (4.2 mmol, 14.0 equiv), catalysts **3c** (20 mol %) and **4c** (40 mol %) in DMSO (0.3 M) at RT. [b]Yield refers to the column-purified product. [c]dr was determined based on ^{1}H NMR or HPLC analysis. [d]ee was determined by CSP-HPLC analysis. [e]ee mentioned for major isomer. [f]Reactions were carried out with **1** (0.3 mmol), cyclohexanone **2a** (3 mmol, 10.0 equiv) with catalysts **3a** (15 mol %) and **4h** (10 mol %) under neat conditions at RT.

Table 4. Asymmetric Desymmetrization of 4-Substituted Cyclohexanone through L-DMTC (3c) and TFA (4c) Catalyzed LLB-A Reactions[a]



entry	product 5	t (h)	yield (%)[b]	dr[c]	ee[d,e]
1	 5ac	36	80	6.2:1	>99
2	 5ad	48	88	13.6:1	99
3	 5ae	24	75	10.7:1	>99
4	 5af	48	55	99:1	99
5	 5ag	36	95	18:1	99

[a]Unless otherwise mentioned, all reactions were carried out with **1a** (0.3 mmol), cyclohexanone **2** (4.2 mmol, 14.0 equiv), catalysts **3c** (20 mol %) and **4c** (40 mol %) in DMSO (0.3 M) at RT. [b]Yield refers to the column-purified product. [c]dr was determined based on ^{1}H NMR or HPLC analysis. [d]ee was determined by CSP-HPLC analysis. [e]ee mentioned for major isomer.

reduced yield, the reactions were also performed with the other catalyst system, **3a**/**4h**, under neat conditions and found to furnish the products with better yields but with reduced dr in a few cases (Table 3, entries 1, 5, and 8).

Asymmetric Synthesis of LLB-A Products 5ac−ag. After studying the scope of the LLB-A reaction with various functionalized *o*-azidobenzaldehydes **1a−i**, we extended our studies further in order to check the generality of the reaction on various 4-substituted cyclohexanones **2c−g**. The 4-alkyl substituted cyclohexanones **2c−2g** on subjecting to LLB-A reaction with *o*-azidobenzaldehyde (**1a**) using the optimized conditions resulted in the products *anti*-(−)-**5ac** to *anti*-(−)-**5ag** in 55−95% yields with good dr and 99% ee (Table 4, entries 1−5). Our choice of 4-substituted cyclohexanone substrates revealed itself the intriguing contribution imparted by the size and bulkiness of the 4-alkyl substituent in controlling the dr of the products in the LLB-A reaction. The size of the 4-alkyl substituent worked as a steric handle in controlling the dr of the product. As the size of the 4-substituent increased, the dr of the product increased too. Another fascinating element of surprise in this scenario was that we observed the exclusive formation of a single enantiomer, resulting in asymmetric desymmetrization[14] of the 4-substituted cyclohexanone substrates under the given reaction conditions. The structure, regioselectivity, and absolute stereochemistry of the LLB-A products **5** and **6** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (−)-**5ca** and (−)-**5ac** as shown in Figures S1 and S2 (see Supporting Information-I).[15]

Controlled Experiments to Study the *ortho*-N_3 Involvement in the *Pre*-transition State. After conducting studies toward the scope and generality of the LLB-A reaction with differently substituted *o*-azidobenzaldehydes and 4-

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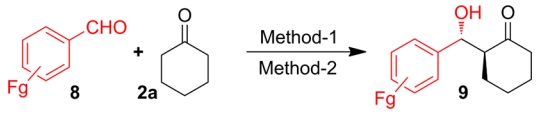
Table 5. Controlled Experiments To Study the Effect of Azido Group in LLB-A Reactions[a]



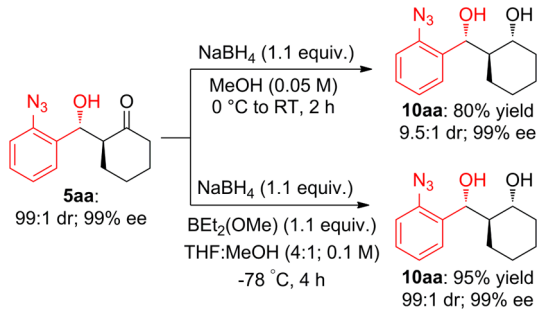
		Method-1			Method-2		
entry	Fg	yield (%)[b]	ee (%)[c,d]	dr[e]	yield (%)[b]	ee (%)[c,d]	dr[e]
1	H (**8a**)	45 (**9aa**)	97	4.4:1	88 (**9aa**)	90	2.2:1
2	3-N_3 (**8b**)	47 (**9ba**)	96	6.3:1	90 (**9ba**)	93	3.4:1
3	4-N_3 (**8c**)	16 (**9ca**)	88	15.6:1	81 (**9ca**)	93	4.5:1

[a]Unless otherwise mentioned, all the reactions were carried out using the Method-1: **3c** (20 mol %) and **4c** (40 mol %) in DMSO (0.3 M), RT, 24 h; or Method-2: **3a** (15 mol %) and **4h** (10 mol %), neat, RT, 24 h. [b]Yield refers to the column-purified product. [c]ee was determined by CSP-HPLC analysis. [d]ee mentioned for major isomer. [e]dr was determined based on ^{1}H NMR or HPLC analysis.

substituted cyclohexanone substrates, at this juncture, we turned our attention to examine the involvement of the azido group of the *o*-azidobenzaldehydes in the *pre*-transition state, for which we performed some controlled experiments (Table 5). In the absence of the *o*-azido group, meaning simple benzaldehyde (**8a**) underwent LLB-A reaction under the catalysis of **3c**/**4c** (Method-1) with cyclohexanone (**2a**) to furnish the product *anti*-(+)-**9aa** in reduced (45%) yield with 97% ee and 4.4:1 dr (Table 5, entry 1). Likewise, 3-azidobenzaldehyde (**8b**) gave the product *anti*-(+)-**9ba** in almost similar yield and ee with slightly better dr, while 4-azidobenzaldehyde (**8c**) provided the product *anti*-(+)-**9ca** in low yield with a noticeable decrease in ee, though there was an increase in dr (Table 5, entries 2 and 3). *These results on comparison with that of o-azidobenzaldehyde (**1a**) (Table 1, entry 13) provide insight into the fact that indeed the o-azido group plays a vital role in the pre-transition state to control the product formation.*[10] Moreover, these controlled experiments were also conducted via Method-2 (Table 5) using **3a**/**4h** under neat conditions, which provided the products *anti*-(+)-**9aa** to *anti*-(+)-**9ca** in more or less similar yields but with deteriorated ee and dr when compared with result for *o*-azidobenzaldehyde (**1a**) (Table 1, entry 25), which is again in accordance with our explanation. A more detailed description of the participation from the *o*-azido group will be provided later during the mechanistic studies. Structure and regioselectivity of LLB-A products **9** were obtained based on the NMR analyses and also by correlation with previous L-proline-catalyzed LLB-A reactions (Figure S3; see Supporting Information-I).[2]

Applications of Chiral LLB-A Products. *Asymmetric Synthesis of syn-(+)-1,3-Diols.* As organic chemists, we felt that our investigation would be incomplete and futile without applications. Subsequently, we sought after some application oriented studies on the derived LLB-A products. First, we wanted to reduce the LLB-A product, keto-alcohol *anti*-(−)-**5aa**, to the dihydroxy compound (+)-**10aa**, as chiral *syn*-diols are important as chiral ligands for many asymmetric reactions. Simple sodium borohydride reduction at 0−25 °C on the keto-alcohol *anti*-(−)-**5aa** furnished the *syn*-diol (+)-**10aa** in 80% yield with 99% ee, but with reduced 9.5:1 dr (Scheme 2). On the contrary, when the same sodium borohydride reduction was carried out in the presence of 1.1 equiv of Lewis acid BEt_2OMe at −78 °C, the product was formed in 95% yield, absolutely as a single isomer with an optical purity of 99%, the reason being the interaction of the Lewis acid with both keto and hydroxy groups, resulting in the transfer of hydride from the face opposite to that of the hydroxy group so as to produce the *syn*-diol (+)-**10aa** extraordinarily (Scheme 2). The *syn*-diol

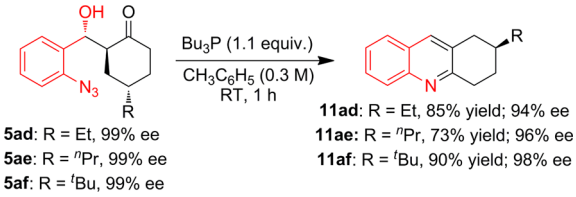
Scheme 2. Asymmetric Synthesis of *syn*-(+)-1,3-Diol 10aa from *anti*-(−)-5aa



(+)-**10aa** possessing an azido group could be easily converted to a chiral amino-diol, which could serve as potent chiral ligand (Scheme 2).

Asymmetric Synthesis of Functionalized Tetrahydroacridines from LLB-A Products. Second, the LLB-A products *anti*-(−)-**5ad**−**5af** were converted to alkyl substituted tetrahydroacridines (−)-**11ad**−**11af**, by treating them with 1.1 equiv of tributylphosphine in toluene at RT for 1 h. In this cascade reaction, tributylphosphine initially reacted with the azido group to generate an iminophosphorane intermediate, which underwent an in situ intramolecular aza-Wittig reaction with the keto group, followed by in situ elimination of the hydroxyl group as water, resulted in aromatization to furnish the alkyl substituted chiral (−)-tetrahydroacridines in very good yields, which were found to be materialistically and medicinally important compounds (Scheme 3).[16] Three different tetrahydroacridines (−)-**11ad**−**11af** were furnished in good yields with high ee's, but the ee's of (−)-**11ad**−**11af** were slightly decreased compared to those of the starting LLB-A compounds, may be due to the epimerization because of the basic nature of reaction with tributylphosphine and tributylphosphine oxide. It is worth mentioning here that the crude

Scheme 3. Asymmetric Synthesis of Functionalized Tetrahydroacridines 11



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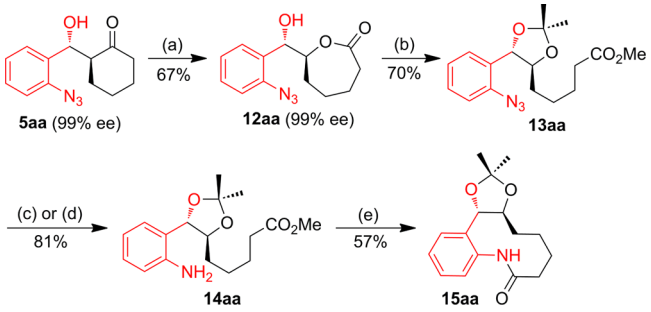
LLB-A products, *anti*-(−)-**5ad**−**5af** gave better yields of tetrahydroacridines (−)-**11ad**−**11af** than the corresponding purified products (Scheme 3).

Asymmetric Synthesis of Structurally Rigid 10-Membered Lactams. Third, we decided to convert the chiral LLB-A products into functionally rich and structurally rigid 10-membered lactams, which could prove to be effective chelating ligands for different metal ions (Scheme 4).[17] Consequently, Baeyer−Villiger oxidation of *anti*-(−)-**5aa** with *m*-CPBA furnished the selective lactone (+)-**12aa** in 67% yield, which, on hydrolysis of the lactone, followed by protection of the resulting diol as acetonide and esterification of the carboxylic acid with ethereal diazomethane solution, generated the azido-ester (−)-**13aa** in 70% yield. Reduction of the azido group to an amino group was effected with either indium chloride and triethylsilane or tributylphosphine to furnish the compound (−)-**14aa**, which, on reaction with potassium tertiary butoxide in dry THF, produced the 10-membered lactam (−)-**15aa** in 57% yield (Scheme 4).

Scheme 4. Asymmetric Synthesis of 10-Membered (−)-Lactam 15aa[a]

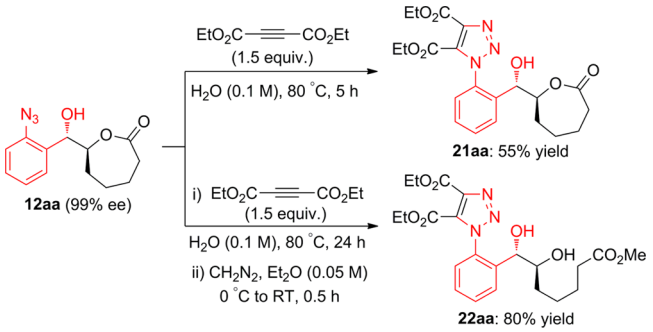


[a]Reaction conditions: (a) mCPBA (3 equiv), $NaHCO_3$ (2 equiv), CH_2Cl_2 (0.1 M), RT, 5 h, 67%; (b) (i) 5% aq. NaOH, MeOH:H_2O (1:1), 80 °C, 1 h; (ii) 2,2-dimethoxypropane (1.4 equiv), *p*-TSA (0.01 equiv), $MgSO_4$ (0.007 equiv), acetone (0.1 M), RT, 4 h; (iii) CH_2N_2, Et_2O, 0−5 °C, 0.5 h, 70% for 3 steps; (c) $InCl_3$ (1.1 equiv), Et_3SiH (2.2 equiv), MeOH (0.05 M), 0 °C to RT, 2 h, 81%; (d) Bu_3P (3 equiv), dry $CH_3C_6H_5$ (0.1 M), RT, 1 h, 71%; (e) *t*BuOK (1.5 equiv), dry THF (0.03 M), RT, 24 h, 57%.

Asymmetric Synthesis of Functionalized Allenone. After opening the doors to a few applications for the LLB-A products, still unsatisfied, we wanted to exploit more from the lactone (+)-**12aa**. As a result, the lactone (+)-**12aa** was subjected to DIBAL-H reduction to furnish the triol (+)-**16aa**, which was converted to the alcohol (+)-**17aa** by protection of two of the hydroxy groups as acetonide. The propargylic alcohol (+)-**19aa**, prepared from the acetonide-alcohol (+)-**17aa** through IBX oxidation and Grignard addition, which, on one-pot oxidation, followed by subsequent isomerization by treatment with PCC, furnished the functionalized allenone (+)-**20aa** in good yield (Scheme 5), which could be an impending substrate for diverse organocatalytic reactions.[18]

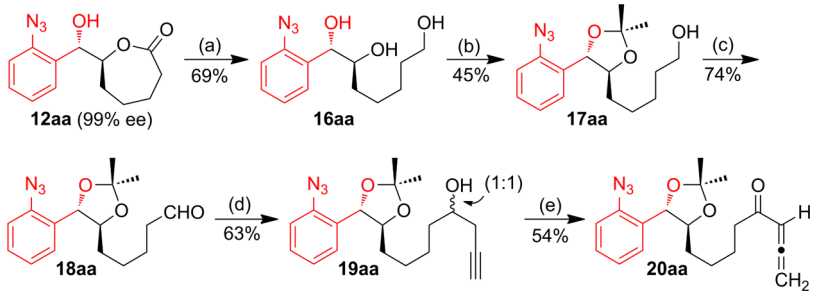
Asymmetric Synthesis of Functionalized 1,2,3-Triazoles. In another direction, the lactone (+)-**12aa**, possessing the functionally important azido group, on treatment with ethyl acetylene dicarboxylate underwent click reaction in water for 5 h to furnish the 1,2,3-triazole (+)-**21aa** in 55% yield,[19] whereas a prolonged reaction time (24 h) resulted in the formation of the 1,2,3-triazole as well as the hydrolysis of the lactone ring to give a carboxylic acid, which was esterified with ethereal diazomethane solution to furnish the 1,2,3-triazole diol-ester (+)-**22aa** with increased yield, 80% (Scheme 6).[19]

Scheme 6. Application of Click Reaction on LLB-A Compounds



Gram-Scale Synthesis of LLB-A Product (−)-5aa. With industrial applications in mind, herein, we have demonstrated the gram-scale synthesis of LLB-A product (−)-**5aa** (Scheme 7). By scaling up milligrams to 1.0 g of *o*-azidobenzaldehyde (**1a**) with 9.8 mL of cyclohexanone (**2a**) in 22.6 mL of DMSO at 25 °C for 24 h under the **3c**/**4c**-catalysis furnished the LLB-A product (−)-**5aa** in 76% conversion with 72% yield, 33:1 dr, and 99% ee. Reaction rate slightly decreased and dr improved in gram-scale synthesis compared to milligram-scale (see Table 1, entry 13), may be due to the slight change in reaction volume (Scheme 7).

Scheme 5. Asymmetric Synthesis of Functionalized (+)-Allenone 20aa[a]



[a]Reaction conditions: (a) DIBAL-H (4 equiv), $CH_3C_6H_5$ (0.5 M), RT, 4 h, 69%; (b) 2,2-dimethoxypropane (1.4 equiv), *p*-TSA (0.01 equiv), $MgSO_4$ (0.007 equiv), acetone (0.15 M), RT, 4 h, 45%; (c) IBX (3 equiv), CH_3CN (0.16 M), 80 °C, 3 h, 74%; (d) prop-2-yn-1-ylmagnesium bromide (1.5 equiv), dry THF (0.03 M), −10 °C to RT, 12 h, 63%; (e) PCC (2 equiv), CH_2Cl_2 (0.04 M), 0 °C to RT, 2 h, 54%.

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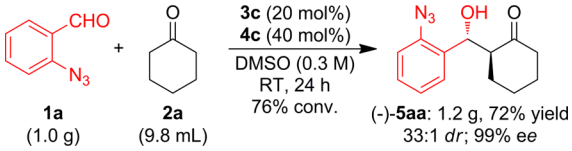
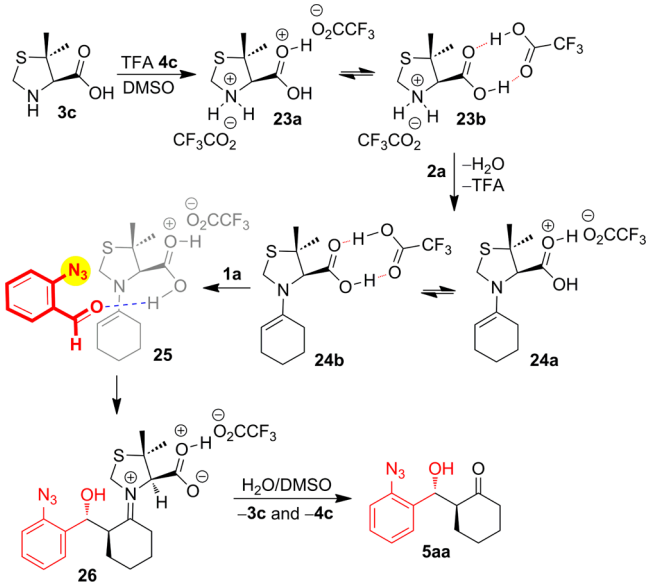
Scheme 7. Gram-Scale Synthesis of LLB-A Product (−)-5aa[a]



[a]Reaction conditions: **1a** (1.0 g, 6.8 mmol), **2a** (9.8 mL, 95.2 mmol), **3c** (219.2 mg, 20 mol %), **4c** (208 μL, 40 mol %), DMSO (22.6 mL, 0.3 M), RT, 24 h.; 76% conversion and 72% yield [90% yield based on the starting material consumed].

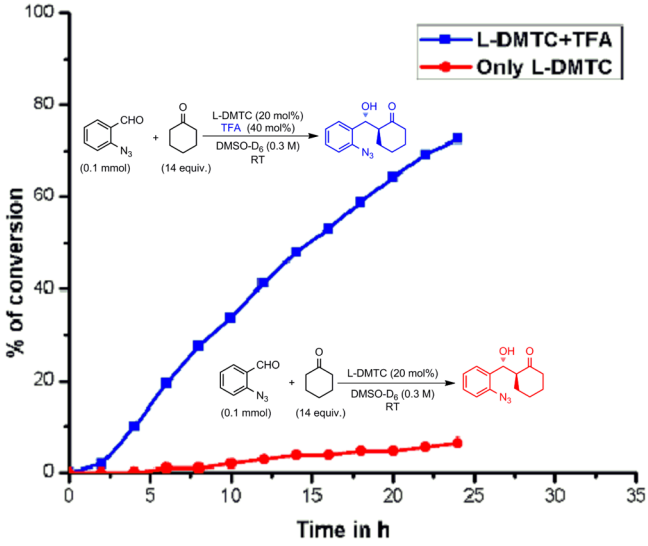
Reaction Mechanism. Herein, we attempted to explain the mechanistic aspects of the synergistic L-DMTC/TFA catalyzed LLB-A reaction based on the few controlled and NMR experiments (Scheme 8). We gathered substantial evidence

Scheme 8. Proposed Reaction Mechanism



from the NMR studies of catalyst combination **3c** and **4c** in DMSO-D_6 that the catalyst L-DMTC (**3c**) coordinates with two molecules of TFA (**4c**) and exists in the ionic cluster form **23a**, which is in equilibrium with **23b** (Scheme 8 and Figure S4; see SI-I). As entire signals in ^{1}H and ^{13}C NMR spectra of **3c** with **4c** are shifted compared to only **3c**, which is due to the strong interaction of both the functional groups of NH and CO_2H with TFA (Figure S4; see Supporting Information-I). We have also done **3c**-catalyzed LLB-A reactions of **1a** and **2a** in DMSO-D_6 with and without TFA (**4c**) in an NMR tube to know the reaction relative rates (Scheme 9 and Figure S5; see SI-I). From the optimization studies, we came to know that DMSO facilitates the LLB-A reaction, most probably due to the stabilization of the synergistic catalyst cluster by interaction of the solvent molecules. From the above experiments, we are proposing that the cyclohexanone **2a** reacts sharply with the catalyst cluster **23a** to form the enamine **24a**, which exists in equilibrium with **24b**. The *o*-azidobenzaldehyde (**1a**) approaches the enamine **24a** from its *Re*-face in such a way that it can anchor by interaction via electrostatic interactions and hydrogen bonding of the azido group and the aldehyde group with the sulfur and carboxylic acid of L-DMTC (**3c**), respectively, so that the *Re*-face of the *o*-azidobenzaldehyde

Scheme 9. NMR Experiments To Find the Relative Rate of LLB-A Reaction under the 3c- and 3c/4c-Catalysis



(**1a**) is facing the *Re*-face of the enamine **24a** for the aldol reaction.[2] Accordingly, this results in the formation of the iminium intermediate **26**, which, on hydrolysis, furnishes the product *anti*-(−)-**5aa**, regenerating the synergistic catalyst L-DMTC (**3c**) and TFA (**4c**). This LLB-A reaction rate and selectivity are completely controlled by catalysts **3c** (pK_a = ~9.76) and **4c** (pK_a = 3.45) structure and their dense interactions based on the pK_a values synergetic in DMSO, which is thoroughly utilized by *o*-azido group interactions.[20]

CONCLUSIONS

In summary, we have described for the first time the L-DMTC/TFA-catalyzed asymmetric LLB-A reaction of cyclohexanones and acetone with less reactive *o*-azidobenzaldehydes at ambient conditions. The LLB-A reaction proceeds in very good yields with high selectivity using a synergistic combination of L-amino acid, L-DMTC with simple Brønsted acid TFA. Furthermore, we have demonstrated the application of chiral LLB-A products *anti*-(−)-**5** in the synthesis of highly functionalized azido-containing molecular scaffolds **9**−**22**. We explained the mechanistic synergy of L-DMTC with TFA to increase the rate and selectivity of LLB-A reaction of **1** and **2** in DMSO-D_6 with the controlled and online NMR experiments. Further work is in progress to utilize chiral LLB-A products, *anti*-(−)-**5** as intermediates for the bioactive molecules synthesis.

EXPERIMENTAL SECTION

General Experimental Procedures for the LLB-A Reactions. *General Methods.* The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 experiment and is given in parentheses. The coupling constants *J* are given in Hz. Column chromatography was performed using silica gel (particle size: 0.063−0.200 mm). High-resolution mass spectra were recorded on a micromass ESI-TOF MS. IR spectra were recorded on FT/IR-5300 and FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo−Kα (λ = 0.71073 Å) radiation with CAD4 software, or the X-ray intensity data were measured at 298

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K on a SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo−Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL), followed by heating.

Materials. All solvents and commercially available chemicals were used as received. The highly functionalized *ortho*-azidobenzaldehydes **1a−i** are prepared according to the literature procedures.[21]

General Procedure for L-DMTC and TFA Catalyzed LLB-A Reaction of Cyclohexanones 2 with 2-Azidobenzaldehydes 1 (Procedure A). In an ordinary glass vial equipped with a magnetic stirring bar, containing L-DMTC (**3c**) (9.7 mg, 0.06 mmol) in DMSO (1.0 mL, 0.3 M), was added TFA (**4c**) (9.2 μL, 0.12 mmol). After stirring for a minute, 2-azidobenzaldehyde (**1**) (0.3 mmol) and cyclohexanone (**2**) (4.2 mmol) were added, and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure LLB-A products **5** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for L-Proline and Guanidinium Tetrafluoroborate Catalyzed LLB-A Reaction of Cyclohexanone 2 with 2-Azidobenzaldehyde 1 (Procedure B). In an ordinary glass vial equipped with a magnetic stirring bar, guanidinium tetrafluoroborate (**4e**) (6.2 mg, 0.03 mmol) and L-proline (**3a**) (5.2 mg, 0.045 mmol) were weighed together. Cyclohexanone (**2**) (3.0 mmol) was added to the solid mixture, followed by addition of 2-azidobenzaldehydes (**1**) (0.3 mmol), and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure LLB-A products **5** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of Double Aldol Product 6ab (Procedure C). In a 10 mL round-bottom flask equipped with a magnetic stirring bar, prolinamide catalyst **3e** (11.0 mg, 0.03 mmol) and $PhCO_2H$ (3.6 mg, 0.03 mmol) were added, followed by addition of acetone (**2b**) (1 mL, 0.3 M). The reaction mixture was cooled to −35 °C. After stirring the reaction mixture at −35 °C for 0.5 h, 2-azidobenzaldehyde (**1a**) (44.1 mg, 0.3 mmol) was added to it, and stirring was continued at the same temperature for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure LLB-A products **5ab** and double-aldol addition product **6ab** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for L-DMTC and TFA Catalyzed LLB-A Reaction of 2a with 8 (Procedure D). In an ordinary glass vial equipped with a magnetic stirring bar, containing L-DMTC (**3c**) (9.7 mg, 0.06 mmol) in DMSO (1.0 mL, 0.3 M), was added TFA (**4c**) (9.2 μL, 0.12 mmol). After stirring for a minute, aldehyde **8** (0.3 mmol) and cyclohexanone (**2a**) (4.2 mmol) were added, and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure LLB-A products **9** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for L-Proline and Guanidinium Tetrafluoroborate Catalyzed LLB-A Reaction of 2a with 8 (Procedure E). In an ordinary glass vial equipped with a magnetic stirring bar, guanidinium tetrafluoroborate (**4e**) (6.2 mg, 0.03 mmol) and L-proline (**3a**) (5.2 mg, 0.045 mmol) were weighed together. Cyclohexanone (**2a**) (3.0 mmol) was added to the solid mixture, followed by addition of aldehydes **8** (0.3 mmol), and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure LLB-A products **9** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Reduction of LLB-A Products 5 (Procedure F). In a 10 mL round-bottom flask equipped with a magnetic stirring bar, compound *anti*-(−)-**5aa** (0.18 mmol) was dissolved in dry MeOH (3.6 mL, 0.05 M) and then cooled to ice salt temperature, followed by addition of $NaBH_4$ (7.5 mg, 0.20 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 0.5 h and then at RT for 1.5 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product (+)-**10aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Lewis Acid Mediated *syn*-Selective Reduction of LLB-A Products 5 (Procedure G). In a 10 mL round-bottom flask equipped with a magnetic stirring bar, compound *anti*-(−)-**5aa** (0.18 mmol) was dissolved in dry THF:MeOH (4:1, 0.1 M) and then cooled to −78 °C, and BEt_2OMe (19.8 mg, 0.20 mmol), and $NaBH_4$ (7.5 mg, 0.20 mmol) were added to it under a nitrogen atmosphere. After stirring the reaction mixture at the same temperature for 4 h, the crude reaction mixture was worked up with slow addition of H_2O_2 solution and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product (+)-**10aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of Chiral 1,2,3,4-Tetrahydroacridine 11 (Procedure H). Crude LLB-A product **5** (0.3 mmol) was dissolved in toluene (1 mL, 0.3 M), followed by addition of Bu_3P (82 μL, 0.33 mmol). The reaction mixture was stirred at 25 °C for 1 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **11** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 12aa (Procedure I). To a solution of chiral product *anti*-(−)-**5aa** (170 mg, 0.7 mmol) in dry DCM (7 mL, 0.1 M) were added successively $NaHCO_3$ (117 mg, 1.4 mmol) and *m*CPBA (362 mg, 2.1 mmol). The reaction mixture was stirred at 25 °C for 5 h. The reaction mixture was worked up with aqueous $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product (+)-**12aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 13aa (Procedure J). To a solution of chiral product *anti*-(+)-**12aa** (300 mg, 1.1 mmol) in MeOH (6 mL) was added aqueous 5% NaOH solution (6 mL). The reaction mixture was heated to reflux at 80 °C for 1 h. The reaction mixture was worked up with aqueous 2 N HCl, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude hydrolyzed compound was dissolved in acetone (11 mL, 0.1 M), and $MgSO_4$ (1.0 mg, 0.008 mmol), *p*-TSA·H_2O (1.89 mg, 0.011 mmol), and 2,3-dimethoxypropane (0.19 mL, 1.54 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h. Anhydrous Na_2CO_3 (254 mg, 2.4 mmol) was added to the reaction mixture, then filtered and concentrated. To the crude reaction mixture dissolved in diethyl ether (10 mL, 0.05 M) was added diazomethane in ether solution at 0−5 °C for 30 min. Ether was evaporated. Pure product (−)-**13aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

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General Procedure for the Preparation of 14aa (Procedure K). Method-1: To a solution of chiral product (−)-**13aa** (33 mg, 0.1 mmol) in dry toluene (1 mL, 0.1 M) was added Bu_3P (75 μL, 0.3 mmol), and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product (−)-**14aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate). **Method-2**: In an oven-dried round-bottom flask, equipped with magnetic stirring bar, containing $InCl_3$ (15 mg, 0.066 mmol) and triethylsilane (20 μL, 0.13 mmol) in MeOH (2 mL, 0.05 M) at 0 °C was added (−)-**13aa** (0.06 mmol) dissolved in MeOH dropwise. The mixture was stirred at the same temperature for 2 h. The crude reaction mixture was then worked up with water, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product (−)-**14aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 15aa (Procedure L). To a solution of chiral product (−)-**14aa** (20 mg, 0.06 mmol) in dry THF (2 mL, 0.03 M) was added KO*t*Bu (10 mg, 0.09 mmol), and the reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture was treated with saturated aqueous NH_4Cl solution, and then the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure product (−)-**15aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 16aa (Procedure M). To a solution of chiral product (+)-**12aa** (655 mg, 2.5 mmol) in dry toluene (5 mL, 0.5 M) was added DIBAL-H (25% solution in toluene, 6.8 mL, 10.0 mmol), and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with H_2O (10 mL), and sodium potassium (+)-tartrate tetrahydrate (7 g), and ethyl acetate (10 mL) were added. This mixture was stirred vigorously for 1 h and was again diluted with H_2O. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure product (+)-**16aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 17aa (Procedure N). To a solution of chiral product (+)-**16aa** (360 mg, 1.35 mmol) in acetone (9 mL 0.15 M) were added $MgSO_4$ (1.0 mg, 0.009 mmol), *p*-TSA·H_2O (2.3 mg, 0.013 mmol), and 2,3-dimethoxypropane (0.23 mL, 1.89 mmol). The reaction was stirred at 25 °C for 4 h. Anhydrous Na_2CO_3 (254 mg, 2.4 mmol) was added to the reaction mixture. The mixture was filtered and concentrated. Pure product (+)-**17aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 18aa (Procedure O). To a solution of chiral product (+)-**17aa** (240 mg, 0.8 mmol) in CH_3CN (5 mL 0.16 M) was added IBX (672 mg, 2.4 mmol), and the reaction was heated to reflux for 3 h. The reaction mixture was filtered and concentrated. Pure product (+)-**18aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 19aa (Procedure P). Step 1: To a flame-dried flask were added 1.0 g of Mg, 24 mg of $HgCl_2$, and 4 mL of diethyl ether. Propargyl bromide (0.1 mL, 80% in toluene) was added, and the reaction was initiated by heating with a heat gun. The mixture was cooled to 0 °C, and a solution of 1.4 mL of propargyl bromide (80% in toluene) in 8 mL of ether was slowly added over 1 h. The reaction was stirred at 0 °C for 0.5 h and allowed to settle at 0 °C for 0.5 h to give an ∼1 M solution.

Step 2: To a solution of chiral product (+)-**18aa** (250 mg, 0.82 mmol) in dry THF (26 mL 0.03 M) at −10 °C was added propargyl magnesium bromide (1.2 mL, 1 M solution in ether, 1.2 mmol). The reaction mixture was stirred at the same temperature for 30 min and then brought to room temperature and stirred for another 12 h. The crude reaction mixture was treated with saturated aqueous NH_4Cl solution, and then the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure products (+)-**19aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 20aa (Procedure Q). To a solution of chiral product (+)-**19aa** (70 mg, 0.2 mmol) in DCM (5 mL 0.04 M) at 0 °C was added PCC (86.2 mg, 0.4 mmol). The reaction mixture after being stirred at the same temperature for 30 min was brought to room temperature and stirred for an additional 2 h. The crude reaction mixture was passed through a pad of Celite and concentrated to dryness. Pure chiral products (+)-**20aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 21aa (Procedure R). To a solution of chiral product (+)-**12aa** (25 mg, 0.1 mmol) in H_2O (1 mL, 0.1 M) was added diethyl acetylenedicarboxylate (25.5 mg, 0.15 mmol), and the reaction was stirred at 70 °C for 5 h. The crude reaction mixture was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure products (+)-**21aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Preparation of 22aa (Procedure S). To a solution of chiral product (+)-**12aa** (25 mg, 0.1 mmol) in H_2O (1 mL, 0.1 M) was added diethyl acetylenedicarboxylate (25.5 mg, 0.15 mmol), and the reaction was stirred at 70 °C for 12 h. The crude reaction mixture was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. To the crude reaction mixture dissolved in diethyl ether (10 mL, 0.05 M) was added diazomethane in ether solution at 0−5 °C for 0.5 h. Ether was evaporated in a fume wood. Pure products (+)-**22aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for the Gram-Scale Synthesis of (−)-5aa (Procedure T). In an 100 mL round-bottom flask equipped with a magnetic stirring bar, containing L-DMTC (**3c**) (219.2 mg, 1.36 mmol, 20 mol %) in DMSO (22.6 mL, 0.3 M), was added TFA (**4c**) (208 μL, 2.72 mmol, 40 mol %). After stirring for a minute, 2-azidobenzaldehyde (**1a**) (1.0 g, 6.8 mmol) and cyclohexanone (**2a**) (9.8 mL, 95.2 mmol) were added, and the reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture was then worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure LLB-A product (−)-**5aa** (1.2 g, 72%) and starting material **1a** (200 mg, 20%) were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

*(S)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)cyclohexanone (**5aa**).* Prepared following the procedures **A** and **B** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 88% (64.7 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 18.13 min (major), t_R = 25.32 min (minor); $[\alpha]_D^{25} = -4.3°$ (*c* = 0.44, $CHCl_3$, 99% ee/de); IR (Neat): ν_{max} 3507 (OH), 2931, 2855, 2126 (N_3), 1699 (C═O), 1584, 1490, 1447, 1310, and 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (1H, dd, *J* = 7.6, 1.2 Hz), 7.25 (1H, dt, *J* = 8.0, 1.6 Hz), 7.10 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 5.08 (1H, d, *J* = 8.4 Hz), 3.87 (1H, br s, O*H*), 2.64−2.58 (1H, m), 2.42−2.36 (1H, m), 2.27 (1H, dt, *J* = 12.8, 5.6 Hz), 2.02−1.97 (1H, m), 1.75−1.72 (1H, m), 1.63−1.37 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*═O), 137.3 (C), 132.6 (C), 128.8 (CH), 128.2 (CH), 125.1 (CH), 117.8 (CH), 68.9 (CH), 57.1 (CH), 42.6 (CH_2), 30.4 (CH_2), 27.7 (CH_2), 24.7 (CH_2); HRMS *m*/*z* 268.1061 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

*(R)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)cyclohexanone (**5aa**).* Prepared following the procedures **A** and **B** and purified by column chromatography using EtOAc/hexane (1:9) and isolated as a solid; Yield: 60% (44.2 mg); Mp 74−78 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5

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mL/min, λ = 254 nm), t_R = 17.07 min (minor), t_R = 19.64 min (major); $[\alpha]_D^{25}$ = −144.5° (*c* = 0.29, $CHCl_3$, 96% ee); IR (Neat): ν_{max} 3496 (OH), 2937, 2860, 2115 (N_3), 1699 (C═O), 1584, 1490, 1452, 1293, 1129, 1074, 981, and 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (1H, dd, *J* = 8.0, 0.5 Hz), 7.30 (1H, dt, *J* = 7.5, 1.5 Hz), 7.16 (1H, dt, *J* = 7.5, 0.5 Hz), 7.12 (1H, dd, *J* = 7.5, 1.0 Hz), 5.53 (1H, d, *J* = 1.0 Hz), 3.16 (1H, s, O*H*), 2.75 (1H, m), 2.48−2.37 (2H, m), 2.11−2.06 (1H, m), 1.86−1.82 (1H, m), 1.76−1.50 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.9 (C, *C*═O), 135.5 (C), 132.4 (C), 128.07 (CH), 128.06 (CH), 124.6 (CH), 117.6 (CH), 66.3 (CH), 54.3 (CH), 42.6 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 24.8 (CH_2); HRMS *m*/*z* 268.1061 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

(S)-2-((R)-(2-Azido-4-fluorophenyl)(hydroxy)methyl)cyclohexanone (**5ba**). Prepared following the procedures **A** and **B** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 75% (59.0 mg); Mp 64−66 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.27 min (major), t_R = 12.40 min (minor); $[\alpha]_D^{25}$ = −0.7° (*c* = 0.86, $CHCl_3$, 99% ee, 17:1 dr); IR (Neat): ν_{max} 3457 (OH), 2959, 2920, 2849, 2120 (N_3), 1704 (C═O), 1594, 1457, 1375, 1299, and 959 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (1H, dd, *J* = 8.4, 6.4 Hz), 6.87 (1H, dt, *J* = 8.4, 2.4 Hz), 6.84 (1H, dd, *J* = 11.6, 2.4 Hz), 5.09 (1H, d, *J* = 8.4 Hz), 3.98 (1H, s, O*H*), 2.66−2.59 (1H, m), 2.48−2.44 (1H, m), 2.33 (1H, dt, *J* = 12.8, 5.6 Hz), 2.10−2.06 (1H, m), 1.83−1.80 (1H, m), 1.72−1.39 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*═O), 162.5 (C, d, *J* = 247.0 Hz), 138.9 (C, d, *J* = 9.0 Hz), 129.8 (CH, d, *J* = 9.0 Hz), 128.5 (C, d, *J* = 3.0 Hz), 112.3 (CH, d, *J* = 22.0 Hz), 105.0 (CH, d, *J* = 25.0 Hz), 68.4 (CH), 57.1 (CH), 42.5 (CH_2), 30.3 (CH_2), 27.7 (CH_2), 24.7 (CH_2); HRMS *m*/*z* 286.0968 (M + Na), calcd for $C_{13}H_{14}FN_3O_2Na$ 286.0968.

(S)-2-((R)-(2-Azido-4-chlorophenyl)(hydroxy)methyl)cyclohexanone (**5ca**). Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid. Yield: 89% (75.0 mg); Mp 63−65 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.45 min (major), t_R = 10.30 min (minor); $[\alpha]_D^{25}$ = −5.3° (*c* = 0.87, $CHCl_3$, 98% ee, 17:1 dr); IR (Neat): ν_{max} 3523 (OH), 2959, 2942, 2866, 2126 (N_3), 1688 (C═O), 1573, 1490, 1408, 1304, 1266, 1096, 1047, and 871 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 8.4 Hz), 7.15 (1H, d, *J* = 8.0 Hz), 7.11 (1H, s), 5.09 (1H, br d, *J* = 5.6 Hz), 3.96 (1H, br d, *J* = 2.4 Hz), 2.65−2.59 (1H, m), 2.48−2.45 (1H, m), 2.33 (1H, dt, *J* = 12.8, 5.6 Hz), 2.10−2.08 (1H, m), 1.84−1.81 (1H, m), 1.72−1.47 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*═O), 138.6 (C), 134.3 (C), 131.3 (C), 129.5 (CH), 125.4 (CH), 117.9 (CH), 68.5 (CH), 57.1 (CH), 42.6 (CH_2), 30.4 (CH_2), 27.7 (CH_2), 24.8 (CH_2); HRMS *m*/*z* 302.0673 (M + Na), calcd for $C_{13}H_{14}ClN_3O_2Na$ 302.0672.

(S)-2-((R)-(2-Azido-5-chlorophenyl)(hydroxy)methyl)cyclohexanone (**5da**). Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid. Yield: 90% (76.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 6.53 min (major), t_R = 7.72 min (minor) [for minor *syn*-isomer], t_R = 10.36 min (major), t_R = 12.35 min (minor) [for major *anti*-isomer]; $[\alpha]_D^{25}$ = −11.2° (*c* = 0.93, $CHCl_3$, 99% ee and 51:1 dr); IR (Neat): ν_{max} 3512 (OH), 2937, 2860, 2120 (N_3), 2088, 1699 (C═O), 1479, 1408, 1293, 1112, 1036, 899, and 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (1H, d, *J* = 2.4 Hz), 7.20 (1H, dd, *J* = 8.8, 2.4 Hz), 6.98 (1H, d, *J* = 8.4 Hz), 5.03 (1H, d, *J* = 8.4 Hz), 3.93 (1H, br s O*H*), 2.56−2.50 (1H, m), 2.40−2.34 (1H, m), 2.26 (1H, dt, *J* = 12.8, 6.0 Hz), 2.03−1.96 (1H, m), 1.76−1.73 (1H, m), 1.64−1.37 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.9 (C, *C*═O), 135.8 (C), 134.4 (C), 130.6 (C), 128.7 (CH), 128.3 (CH), 118.9 (CH), 68.4 (CH), 57.1 (CH), 42.5 (CH_2), 30.2 (CH_2), 27.6 (CH_2), 24.6 (CH_2); HRMS *m*/*z* 302.0674 (M + Na), calcd for $C_{13}H_{14}ClN_3O_2Na$ 302.0672.

(S)-2-((R)-(2-Azido-5-bromophenyl)(hydroxy)methyl)cyclohexanone (**5ea**). Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid. Yield: 79% (77.0 mg); Mp 99−102 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.44 min (major), t_R = 17.93 min (minor); $[\alpha]_D^{25}$ = −13.1° (*c* = 0.60, $CHCl_3$, > 99% ee, 17:1 dr); IR (Neat): ν_{max} 3457 (OH), 2937, 2866, 2126 (N_3), 1688 (C═O), 1474, 1293, and 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (1H, d, *J* = 1.6 Hz), 7.42 (1H, dd, *J* = 8.4, 2.0 Hz), 7.00 (1H, d, *J* = 8.4 Hz), 5.10 (1H, d, *J* = 8.4 Hz), 4.00 (1H, br s, O*H*), 2.63−2.57 (1H, m), 2.48−2.45 (1H, m), 2.33 (1H, dt, *J* = 12.8, 6.0 Hz), 2.11−2.07 (1H, m), 1.83−1.81 (1H, m), 1.72−1.47 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.0 (C, *C*═O), 136.4 (C), 134.7 (C), 131.7 (CH), 131.3 (CH), 119.3 (CH), 118.3 (C), 68.4 (CH), 57.2 (CH), 42.6 (CH_2), 30.3 (CH_2), 27.6 (CH_2), 24.7 (CH_2); HRMS *m*/*z* 346.0167 (M + Na), calcd for $C_{13}H_{14}BrN_3O_2Na$ 346.0167.

(S)-2-((R)-(2,4-Diazidophenyl)(hydroxy)methyl)cyclohexanone (**5fa**). Prepared following the procedures **A** and **B**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 41% (35.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.99 min (minor), t_R = 6.55 min (major) [for minor *syn*-isomer], t_R = 9.37 min (major), t_R = 10.60 min (minor) [for major *anti*-isomer]; $[\alpha]_D^{25}$ = −26.5° (*c* = 0.50, $CHCl_3$, 98% ee, 99:1 dr); IR (Neat): ν_{max} 3457 (OH), 2981, 2937, 2904, 2115 (N_3), 1748 (C═O), 1447, 1370, 1244, 1047, and 844 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (1H, d, *J* = 8.4 Hz), 6.80 (1H, dd, *J* = 8.4, 2.0 Hz), 6.66 (1H, d, *J* = 2.0 Hz), 5.02 (1H, d, *J* = 8.4 Hz), 3.88 (1H, br s, O*H*), 2.59−2.53 (1H, m), 2.41−2.38 (1H, m), 2.27 (1H, dt, *J* = 12.8, 5.6 Hz), 2.04−1.99 (1H, m), 1.77−1.74 (1H, m), 1.66−1.37 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, C═O), 140.7 (C), 138.8 (C), 129.6 (CH), 129.4 (C), 115.7 (CH), 108.3 (CH), 68.5 (CH), 57.1 (CH), 42.6 (CH_2), 30.4 (CH_2), 27.7 (CH_2), 24.7 (CH_2); HRMS *m*/*z* 309.1072 (M + Na), calcd for $C_{13}H_{14}N_6O_2Na$ 309.1076.

(S)-2-((R)-(2-Azido-4-(trifluoromethyl)phenyl)(hydroxy)methyl)-cyclohexanone (**5ga**). Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid. Yield: 85% (80.0 mg); Mp 70−72 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.82 min (major), t_R = 12.32 min (minor); $[\alpha]_D^{25}$ = +4.5° (*c* = 1.01, $CHCl_3$, >99% ee, 17:1 dr); IR (Neat): ν_{max} 3468 (OH), 2959, 2871, 2120 (N_3), 1693 (C═O), 1589, 1425, 1331, 1293, 1123, and 866 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 8.0 Hz), 7.35 (1H, br d, *J* = 8.0 Hz), 7.27 (1H, s), 5.08 (1H, d, *J* = 8.0 Hz), 4.00 (1H, br s, O*H*), 2.58−2.56 (1H, m), 2.40−2.36 (1H, m), 2.26 (1H, ddt, *J* = 13.0, 6.0, 0.5 Hz), 2.04−2.00 (1H, m), 1.77−1.75 (1H, m), 1.62−1.45 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.9 (C, *C*═O), 138.0 (C), 136.6 (C), 131.1 (C, q, *J* = 33.7 Hz), 128.9 (CH), 123.4 (C, q, *J* = 282.5 Hz), 121.8 (CH, q, *J* = 3.7 Hz), 114.6 (CH, q, *J* = 2.5 Hz), 68.6 (CH), 57.0 (CH), 42.6 (CH_2), 30.5 (CH_2), 27.7 (CH_2), 24.7 (CH_2); HRMS *m*/*z* 336.0929 (M + Na), calcd for $C_{14}H_{14}F_3N_3O_2Na$ 336.0936.

3-Azido-4-((R)-hydroxy((S)-2-oxocyclohexyl)methyl)benzonitrile (**5ha**). Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 90% (73.0 mg); Mp 78−80 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.37 min (major), t_R = 11.57 min (minor) [for minor *syn*-isomer], t_R = 12.71 min (major), t_R = 17.12 min (minor) [for major *anti*-isomer]; $[\alpha]_D^{25}$ = −1.5° (*c* = 0.96, $CHCl_3$, 99% ee, 21:1 dr); IR (Neat): ν_{max} 3425 (OH), 2942, 2866, 2236 (CN), 2110 (N_3), 1688 (C═O), 1567, 1501, 1414, 1293, 1041, and 888 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (1H, d, *J* = 8.0 Hz), 7.44 (1H, dd, *J* = 8.0, 0.8 Hz), 7.36 (1H, d, *J* = 1.2 Hz), 5.11 (1H, d, *J* = 7.2 Hz), 4.06 (1H, d, *J* = 2.4 Hz), 2.64−2.58 (1H, m), 2.44−2.41 (1H, m), 2.31 (1H, dt, *J* = 12.8, 5.6 Hz), 2.10−2.06 (1H, m), 1.83 (1H, br s), 1.71−1.49 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 214.6 (C, C═O),

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138.4 (C), 138.2 (C), 129.2 (CH), 128.4 (CH), 120.8 (CH), 117.6 (C), 112.4 (C), 68.5 (CH), 56.7 (CH), 42.5 (CH_2), 30.4 (CH_2), 27.6 (CH_2), 24.6 (CH_2); HRMS m/z 293.1014 (M + Na), calcd for $C_{14}H_{14}N_4O_2Na$ 293.1014.

*(S)-2-((R)-(6-Azidobenzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-cyclohexanone (**5ia**).* Prepared following the procedures **A** and **B**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 46% (40.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.50 min (minor), t_R = 19.07 min (major); $[\alpha]_D^{25}$ = −9.0° (*c* = 0.20, $CHCl_3$, 97% ee, 17:1 dr); IR (Neat): ν_{max} 3512 (OH), 2920, 2855, 2110 (N_3), 1688 (C═O), 1479, 1233, 1123, 1047, and 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (1H, s), 6.63 (1H, s), 5.97 (2H, dd, *J* = 4.0, 1.0 Hz), 5.12 (1H, d, *J* = 9.0 Hz), 2.58−2.52 (1H, m), 2.49−2.44 (1H, m), 2.33(1H, ddt, *J* = 14.0, 6.0, 1.0 Hz), 2.09−2.04 (1H, m), 1.83−1.80 (1H, m), 1.72−1.37 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.4 (C, *C*═O), 148.0 (C), 145.5 (C), 130.6 (C), 125.8 (C), 107.5 (CH), 101.7 (CH_2), 98.7 (CH), 68.3 (CH), 57.4 (CH), 42.6 (CH_2), 30.2 (CH_2), 27.7 (CH_2), 24.8 (CH_2); HRMS m/z 312.0955 (M + Na), calcd for $C_{14}H_{15}N_3O_4Na$ 312.0960.

*(R)-4-(2-Azidophenyl)-4-hydroxybutan-2-one (**5ab**).*[21d] Prepared following the procedures **A** and **B**. Purified by column chromatography using EtOAc/hexane (1:9) and isolated as a liquid; Yield: 21% (13.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), t_R = 7.90 min (major), t_R = 8.76 min (minor); $[\alpha]_D^{25}$ = +26.8° (*c* = 0.07, $CHCl_3$, 85% ee); IR (Neat): ν_{max} 3427 (OH), 2961, 2923, 2122 (N_3), 1704 (C═O), 1489, 1299, 1062, and 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (1H, d, *J* = 8.0 Hz), 7.31 (1H, dt, *J* = 8.0, 1.6 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 7.12 (1H, d, *J* = 8.0 Hz), 5.33 (1H, dd, *J* = 9.6, 2.4 Hz), 4.01 (1H, br s, O*H*), 2.88 (1H, dd, *J* = 17.6, 2.8 Hz), 2.72 (1H, dd, *J* = 17.6, 9.6 Hz), 2.20 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.2 (C, *C*═O), 135.8 (C), 133.7 (C), 128.5 (CH), 126.8 (CH), 125.0 (CH), 117.7 (CH), 65.1 (CH), 50.4 (CH_2), 30.5 (CH_3); HRMS m/z 228.0752 (M + Na), calcd for $C_{10}H_{11}N_3O_2Na$ 228.0749.

*(2S,4S)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)-4-methylcyclohexanone (**5ac**).* Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 80% (62.0 mg); Mp 62−64 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 28.76 min (major), t_R = 36.47 min (minor); $[\alpha]_D^{25}$ = −27.4° (*c* = 0.71, $CHCl_3$, 99% ee, 6:1 dr); IR (Neat): ν_{max} 3392 (OH), 2964, 2926, 2849 2120 (N_3), 1699 (C═O), 1589, 1496, 1452, 1304, and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (1H, dd, *J* = 7.6, 0.8 Hz), 7.34 (1H, dt, *J* = 8.0, 1.6 Hz), 7.19−7.14 (2H, m), 5.18 (1H, d, *J* = 8.4 Hz), 3.58 (1H, d, *J* = 3.2 Hz), 2.83 (1H, q, *J* = 8.8 Hz), 2.49−2.45 (2H, m), 2.17−2.10 (1H, m), 2.01−1.93 (1H, m), 1.72−1.58 (2H, m), 1.36−1.25 (1H, m), 1.03 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.1 (C, C═O), 137.3 (C), 132.6 (C), 129.0 (CH), 128.3 (CH), 125.2 (CH), 117.9 (CH), 69.5 (CH), 53.7 (CH), 38.3 (CH_2), 36.1 (CH_2), 33.6 (CH_2), 26.8 (CH), 18.9 (CH_3); HRMS m/z 282.1218 (M + Na), calcd for $C_{14}H_{17}N_3O_2Na$ 282.1218.

*(2S,4S)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)-4-ethylcyclohexanone (**5ad**).* Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 88% (72.0 mg); Mp 85−89 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 8.95 min (major), t_R = 10.22 min (minor); $[\alpha]_D^{25}$ = −36.3° (*c* = 0.74, $CHCl_3$, 99% ee, 14:1 dr); IR (Neat): ν_{max} 3402 (OH), 2969, 2915, 2849, 2131 (N_3), 1709 (C═O), 1577, 1490, 1446, 1287, 1106, 1035, 766, and 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (1H, br d, *J* = 8.0 Hz), 7.34 (1H, br t, *J* = 8.0 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 5.18 (1H, d, *J* = 8.8 Hz), 3.57 (1H, d, *J* = 2.8 Hz), 2.78 (1H, q, *J* = 5.6 Hz), 2.45 (2H, t, *J* = 6.8 Hz), 1.99−1.92 (1H, m), 1.83−1.68 (2H, m), 1.62−1.55 (1H, m), 1.48−1.30 (3H, m), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, C═O), 137.3 (C), 132.6 (C), 129.1 (CH), 128.3 (CH), 125.2 (CH), 117.9 (CH), 69.5 (CH), 53.8 (CH), 38.5 (CH_2), 33.7 (CH), 33.6 (CH_2), 31.4 (CH_2), 25.6 (CH_2), 11.9 (CH_3); HRMS m/z 296.1378 (M + Na), calcd for $C_{15}H_{19}N_3O_2Na$ 296.1375.

*(2S,4S)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)-4-propylcyclohexanone (**5ae**).* Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 75% (64.6 mg); Mp 78−81 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 16.69 min (major), t_R = 18.57 min (minor); $[\alpha]_D^{25}$ = −20.8° (*c* = 0.88, $CHCl_3$, >99% ee, 11:1 dr); IR (Neat): ν_{max} 3402 (OH), 2959, 2926, 2843, 2127 (N_3), 2098, 1707 (C═O), 1577, 1484, 1296, 1172, 1035, 759, and 684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (1H, d, *J* = 7.6 Hz), 7.34 (1H, t, *J* = 7.2 Hz), 7.19−7.14 (2H, m), 5.18 (1H, d, *J* = 8.8 Hz), 3.60 (1H, s, O*H*), 2.78 (1H, q, *J* = 8.8 Hz), 2.45 (2H, t, *J* = 6.4 Hz), 1.98−1.91 (2H, m), 1.71−1.67 (1H, m), 1.60−1.54 (1H, m), 1.42−1.16 (5H, m), 0.88 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*═O), 137.3 (C), 132.6 (C), 129.0 (CH), 128.3 (CH), 125.2 (CH), 117.9 (CH), 69.4 (CH), 54.0 (CH), 38.5 (CH_2), 35.2 (CH_2), 34.1 (CH_2), 31.7 (CH_2), 31.6 (CH), 20.4 (CH_2), 14.1 (CH_3); HRMS m/z 288.1712 (M + H), calcd for $C_{16}H_{21}N_3O_2H$ 288.1712.

*(2S,4S)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)-4-(tert-butyl)-cyclohexanone (**5af**).* Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 55% (50.0 mg); Mp 145−148 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.33 min (minor), t_R = 23.30 min (major); $[\alpha]_D^{25}$ = −73.6° (*c* = 0.23, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3436 (OH), 2959, 2926, 2849, 2126 (N_3), 1720 (C═O), 1468, 1375, 1288, and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, dd, *J* = 8.0, 1.6 Hz), 7.36 (1H, dt, *J* = 7.6, 1.2 Hz), 7.20−7.16 (2H, m), 5.21 (1H, d, *J* = 10.0 Hz), 3.18 (1H, br s, O*H*), 2.82−2.77 (1H, m), 2.61−2.52 (1H, m), 2.48−2.43 (1H, m), 2.08−2.01 (1H, m), 1.07−1.67 (1H, m), 1.57−1.37 (3H, m), 0.80 (9H, s, 3 × CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.3 (C, *C*═O), 137.3 (C), 132.6 (C), 129.3 (CH), 128.6 (CH), 125.2 (CH), 118.1 (CH), 70.1 (CH), 55.5 (CH), 41.8 (CH), 39.2 (CH_2), 32.6 (C), 28.3 (CH_2), 27.1 (3 × CH_3), 26.2 (CH_2); HRMS m/z 324.1688 (M + Na), calcd for $C_{17}H_{23}N_3O_2Na$ 324.1688.

*(2S,4S)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)-4-(tert-pentyl)-cyclohexanone (**5ag**).* Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 95% (90.0 mg); Mp 116−120 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.47 min (minor), t_R = 20.75 min (major); $[\alpha]_D^{25}$ = −48.4° (*c* = 0.29, $CHCl_3$, 99% ee, 18:1 dr); IR (Neat): ν_{max} 3386 (OH), 2970, 2926, 2877, 2120 (N_3), 2098, 1680 (C═O), 1496, 1310, 1041, and 767 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.21−7.17 (2H, m), 5.21 (1H, dd, *J* = 9.5, 5.2 Hz), 3.17 (1H, d, *J* = 5.6 Hz), 2.86−2.80 (1H, m), 2.59−2.50 (2H, m), 2.00−1.97 (1H, m), 1.81−1.74 (1H, m), 1.61−1.43 (3H, m), 1.29−1.11 (2H, m), 0.81 (3H, t, *J* = 7.6 Hz), 0.73 (3H, s, CH_3), 0.71 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.5 (C, *C*═O), 137.3 (C), 132.5 (C), 129.3 (CH), 128.6 (CH), 125.2 (CH), 118.1 (CH), 70.1 (CH), 55.1 (CH), 39.5 (CH), 39.3 (CH_2), 35.0 (C), 32.3 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 23.7 (CH_3), 23.6 (CH_3), 8.0 (CH_3); HRMS m/z 338.1845 (M + Na), calcd for $C_{18}H_{25}N_3O_2Na$ 338.1844.

*(1R,5R)-1,5-bis(2-Azidophenyl)-1,5-dihydroxypentan-3-one (**6ab**).* Prepared following the procedure **C** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a solid; Yield: 21% (22.2 mg); Mp 58−62 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), t_R = 20.14 min (major), t_R = 23.48 min (minor); $[\alpha]_D^{25}$ = +57.8° (*c* = 0.34, $CHCl_3$, 99% ee, 99:1 dr); IR

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(Neat): ν_{max} 3403 (OH), 2126 (N_3), 1715 (C═O), 1584, 1490, 1446, 1293, and 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (2H, dd, J = 7.6, 1.2 Hz), 7.33 (2H, dt, J = 7.6, 1.6 Hz), 7.18 (2H, dt, J = 7.6, 1.2 Hz), 7.14 (2H, dd, J = 8.0, 0.8 Hz), 5.40 (1H, d, J = 2.8 Hz), 5.37 (1H, d, J = 2.8 Hz), 3.33 (2H, br s, OH), 2.89 (2H, dd, J = 17.6, 2.8 Hz), 2.80 (2H, dd, J = 17.2, 2.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.8 (C, C═O), 136.0 (2 × C), 133.6 (2 × C), 128.7 (2 × CH), 126.9 (2 × CH), 125.1 (2 × CH), 117.9 (2 × CH), 65.3 (2 × CH), 50.3 (2 × CH_2); HRMS m/z 375.1182 (M + Na), calcd for $C_{17}H_{16}N_6O_3Na$ 375.1182.

*(E)-4-(2-Azidophenyl)but-3-en-2-one (**7ab**).*[21b] Prepared following the procedures **A** and **B**. Purified by column chromatography using EtOAc/hexane (1:18) and isolated as a solid; Yield: 21% (11.8 mg); Mp 88−92 °C; IR (Neat): ν_{max} 2126 (N_3), 2077, 1666 (C═O), 1644, 1622, 1479, 1293, 1260, 986, and 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1H, d, J = 16.4 Hz), 7.60 (1H, d, J = 7.6 Hz), 7.43 (1H, t, J = 7.6 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.16 (1H, t, J = 7.6 Hz), 6.70 (1H, d, J = 9.6 Hz), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.6 (C, C═O), 139.3 (C), 137.6 (CH), 131.5 (CH), 128.6 (CH), 127.8 (CH), 126.0 (C), 125.0 (CH), 118.8 (CH), 27.1 (CH_3); HRMS m/z 210.0642 (M + Na), calcd for $C_{10}H_9N_3ONa$ 210.0643.

*(S)-2-((R)-Hydroxy(phenyl)methyl)cyclohexanone (**9aa**).*[9e] Prepared following the procedures **D** and **E**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 45% (27.6 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 220 nm), t_R = 16.72 min (major), t_R = 20.79 min (minor); $[\alpha]_D^{25}$ = +14.1° (c = 0.37, $CHCl_3$, 97% ee, 4.4:1 dr); IR (Neat): ν_{max} 3501 (OH), 2926, 2860, 1693 (C═O), 1452, 1299, 1129 and 1041; ^1H NMR ($CDCl_3$) δ 7.36−7.26 (5H, m), 4.78 (1H, d, J = 8.8 Hz), 3.97 (1H, s, OH), 2.65−2.58 (1H, m), 2.50−2.46 (1H, m), 2.36 (1H, dt, J = 13.2, 6.0 Hz), 2.10−2.06 (1H, m), 1.80−1.76 (1H, m), 1.69−1.27 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.5 (C, C═O), 140.9 (C), 128.3 (2 × CH), 127.8 (CH), 127.0 (2 × CH), 74.7 (CH), 57.4 (CH), 42.6 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 24.7 (CH_2); HRMS m/z 227.1048 (M + Na), calcd for $C_{13}H_{16}O_2Na$ 227.1048.

*(S)-2-((R)-(3-Azidophenyl)(hydroxy)methyl)cyclohexanone (**9ba**).* Prepared following the procedures **D** and **E**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 47% (34.6 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 13.67 min (major), t_R = 16.73 min (minor); $[\alpha]_D^{25}$ = +7.3° (c = 0.44, $CHCl_3$, 96% ee, 6:1 dr); IR (Neat): ν_{max} 3485 (OH), 2937, 2860, 2400, 2110 (N_3), 1688 (C═O), 1600, 1490, 1441, 1288, 1224, 882, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (1H, t, J = 8.0 Hz), 7.07 (1H, d, J = 7.5 Hz), 7.02 (1H, s), 6.96 (1H, dd, J = 7.5, 1.0 Hz), 4.77 (1H, dd, J = 8.5, 1.5 Hz), 4.03 (1H, d, J = 2.0 Hz), 2.61−2.56 (1H, m), 2.49−2.45 (1H, m), 2.35 (1H, dt, J = 13.0, 5.5 Hz), 2.11−2.07 (1H, m), 1.82−1.79 (1H, m), 1.71−1.52 (3H, m), 1.35−1.25 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, C═O), 143.0 (C), 140.1 (C), 129.6 (CH), 123.7 (CH), 118.5 (CH), 117.4 (CH), 74.3 (CH), 57.2 (CH), 42.6 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.6 (CH_2); HRMS m/z 268.1063 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

*(S)-2-((R)-(4-Azidophenyl)(hydroxy)methyl)cyclohexanone (**9ca**).* Prepared following the procedures **D** and **E**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 16% (12.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.91 min (major), t_R = 9.54 min (minor); $[\alpha]_D^{25}$ = +13.1° (c = 0.13, $CHCl_3$, 88% ee, 16:1 dr); IR (Neat): ν_{max} 3429 (OH), 2934, 2864, 2101 (N_3), 1703 (C═O), 1692, 1606, 1510, 1503, 1284, 1128, 1039, and 834 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz), 4.77 (1H, d, J = 8.8 Hz), 4.00 (1H, s, OH), 2.62−2.54 (1H, m), 2.51−2.46 (1H, m), 2.36 (1H, dt, J = 13.2, 6.0 Hz), 2.13−2.05 (1H, m), 1.82−1.78 (1H, m), 1.72−1.49 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 215.4 (C, C═O), 139.5 (C), 137.8 (C), 128.5 (2 × CH), 119.0 (2 × CH), 74.2 (CH), 57.4 (CH), 42.6 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.7 (CH_2); HRMS m/z 268.1062 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

*(1R,2R)-2-((R)-(2-Azidophenyl)(hydroxy)methyl)cyclohexanol (**10aa**).* Prepared following the procedures **F** and **G**. Purified by column chromatography using EtOAc/hexane (1:4) and isolated as a liquid; Yield: 95% (46.8 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.92 min (major), t_R = 13.58 min (minor); $[\alpha]_D^{25}$ = +4.6° (c = 0.71, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3273 (OH), 2928, 2856, 2121 (N_3), 1583, 1489, 1449, 1290, 1128, 1076, 1006, 907, and 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (1H, br d, J = 7.6 Hz), 7.32 (1H, tt, J = 8.0, 1.2 Hz), 7.17 (1H, t, J = 7.2 Hz), 7.13 (1H, d, J = 8.0 Hz), 4.92 (1H, d, J = 9.2 Hz), 4.36 (2H, br s, O*H*), 3.64 (1H, dt, J = 9.6, 4.4 Hz), 1.97−1.94 (1H, m), 1.71−1.63 (2H, m), 1.54−1.51 (1H, m), 1.34−1.16 (3H, m), 1.07−0.91 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.2 (C), 134.0 (C), 128.8 (CH), 128.7 (CH), 125.2 (CH), 117.7 (CH), 76.4 (CH), 75.3 (CH), 49.9 (CH), 35.2 (CH_2), 27.0 (CH_2), 25.1 (CH_2), 24.5 (CH_2); HRMS m/z 270.1216 (M + Na), calcd for $C_{13}H_{17}N_3O_2Na$ 270.1218.

*(S)-2-Ethyl-1,2,3,4-tetrahydroacridine (**11ad**).* Prepared following the procedure **H** and purified by column chromatography using EtOAc/hexane (1:18) and isolated as a liquid; Yield: 85% (54.0 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 5.80 min (major), t_R = 7.14 min (minor); $[\alpha]_D^{25}$ = −75.2° (c = 0.16, $CHCl_3$, 94% ee); IR (Neat): ν_{max} 2958, 2924, 2874, 2855, 1622, 1493, 1235, 1155, 857, and 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (1H, d, J = 8.4 Hz), 7.80 (1H, s), 7.70 (1H, d, J = 8.0 Hz), 7.60 (1H, dt, J = 6.8, 1.6 Hz), 7.43 (1H, dt, J = 6.8, 0.8 Hz), 3.23 (1H, ddd, J = 18.0, 5.6, 3.6 Hz), 3.13−3.05 (2H, m), 2.60 (1H, dd, J = 16.4, 11.2 Hz), 2.17−2.12 (1H, m), 1.79−1.68 (1H, m), 1.67−1.51 (1H, m), 1.46 (2H, quin, J = 7.2 Hz), 1.02 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 159.3 (C), 146.6 (C), 135.1 (CH), 130.6 (C), 128.5 (CH), 128.2 (CH), 127.1 (C), 126.9 (CH), 125.5 (CH), 35.7 (CH), 35.6 (CH_2), 33.0 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 11.5 (CH_3); HRMS m/z 212.1439 (M + H), calcd for $C_{15}H_{18}N$ 212.1439.

*(S)-2-Propyl-1,2,3,4-tetrahydroacridine (**11ae**).*[16d,c] Prepared following the procedure **H** and purified by column chromatography using EtOAc/hexane (1:18) and isolated as a liquid; Yield: 73% (49.3 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 16.00 min (major), t_R = 18.39 min (minor); $[\alpha]_D^{25}$ = −33.4° (c = 0.33, $CHCl_3$, 96% ee); IR (Neat): ν_{max} 2957, 2926, 2871, 2854, 1716, and 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (1H, d, J = 8.8 Hz), 7.66 (1H, s), 7.57 (1H, d, J = 8.4 Hz), 7.49 (1H, dt, J = 6.8, 0.8 Hz), 7.31 (1H, dt, J = 6.8, 0.8 Hz), 3.13 (1H, ddd, J = 18.0, 5.6, 4.0 Hz), 3.02−2.89 (2H, m), 2.46 (1H, dd, J = 16.4, 10.4 Hz), 2.05−1.94 (1H, m), 1.75−1.68 (1H, m), 1.51−1.41 (1H, m), 1.40−1.25 (4H, m), 0.85 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 159.1 (C), 146.3 (C), 135.1 (CH), 130.5 (C), 128.4 (CH), 128.0 (CH), 127.0 (C), 126.8 (CH), 125.4 (CH), 38.3 (CH_2), 35.7 (CH_2), 33.6 (CH), 32.8 (CH_2), 29.2 (CH_2), 20.0 (CH_2), 14.2 (CH_3); HRMS m/z 226.1596 (M + H), calcd for $C_{16}H_{20}N$ 226.1596.

*(S)-2-(tert-Butyl)-1,2,3,4-tetrahydroacridine (**11af**).*[16c] Prepared following the procedure **H** and purified by column chromatography using EtOAc/hexane (1:18) and isolated as a liquid; Yield: 90% (64.6 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 13.63 min (minor), t_R = 17.78 min (major); $[\alpha]_D^{25}$ = −101.5° (c = 0.36, $CHCl_3$, 98% ee); IR (Neat): ν_{max} 2942, 2860, 1495, 1429, 1366, 1277, and 1261 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (1H, d, J = 6.8 Hz), 7.83 (1H, s), 7.69 (1H, d, J = 6.4 Hz), 7.61 (1H, t, J = 6.8 Hz), 7.43 (1H, t, J = 6.4 Hz), 3.32−3.27 (1H, m), 3.09−3.01 (2H, m), 2.71 (1H, dd, J = 12.8, 9.2 Hz), 2.19−2.15 (1H, m), 1.61−1.50 (2H, m), 1.00 (9H, s, 3 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 159.3 (C), 146.2 (C), 135.5 (CH), 131.3 (C), 128.6 (CH), 128.0 (CH), 127.1 (C), 126.8

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(CH), 125.6 (CH), 44.5 (CH), 34.1 (CH_2), 32.5 (C), 30.7 (CH_2), 27.2 (3 × CH_3), 24.5 (CH_2); HRMS *m/z* 240.1752 (M + H), calcd for $C_{17}H_{21}NH$ 240.1752.

*(S)-7-((S)-(2-Azidophenyl)(hydroxy)methyl)oxepan-2-one (**12aa**).* Prepared following the procedure **I** and purified by column chromatography using EtOAc/hexane (1:3) and isolated as a liquid; Yield: 67% (122.5 mg). The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), t_R = 14.38 min (minor), t_R = 19.84 min (major); $[\alpha]_D^{25}$ = +68.5° (*c* = 0.86, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3386 (OH), 2953, 2920, 2866, 2126 (N_3), 2093, 1726 (C═O), 1584, 1496, 1457, 1304, 1178, 1052, and 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (1H, d, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.19 (1H, t, *J* = 7.6 Hz), 7.16 (1H, d, *J* = 7.6 Hz), 5.00 (1H, d, *J* = 6.4 Hz), 4.36 (1H, t, *J* = 8.0 Hz), 3.20 (1H, br s, O*H*), 2.71−2.66 (1H, m), 2.58 (1H, t, *J* = 12.8 Hz), 1.94−1.89 (2H, m), 1.80−1.45 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 174.8 (C, *C*═O), 137.4 (C), 130.8 (C), 129.4 (CH), 128.5 (CH), 125.2 (CH), 118.0 (CH), 83.8 (CH), 70.9 (CH), 34.8 (CH_2), 30.5 (CH_2), 27.9 (CH_2), 22.8 (CH_2); HRMS *m/z* 284.1011 (M + Na), calcd for $C_{13}H_{15}N_3O_3Na$ 284.1011.

*Methyl 5-((4S,5S)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (**13aa**).* Prepared following the procedure **J** and purified by column chromatography using EtOAc/hexane (1:10) and isolated as a liquid; Yield: 70% (256.7 mg); $[\alpha]_D^{25}$ = −3.3° (*c* = 0.18, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 2981, 2931, 2866, 2131 (N_3), 1742 (C═O), 1584, 1485, 1457, 1381, 1299, 1233, 1162, 1090, and 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (1H, dd, *J* = 7.6, 1.6 Hz), 7.34 (1H, dt, *J* = 8.0, 1.6 Hz), 7.20−7.14 (2H, m), 4.94 (1H, d, *J* = 8.4 Hz), 3.75−3.70 (1H, m), 3.65 (3H, s, OCH_3), 2.30 (2H, t, *J* = 7.6 Hz), 1.66−1.61 (5H, m), 1.55 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.42−1.26 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 174.0 (C, *C*═O), 137.8 (C), 129.3 (CH), 129.1 (C), 128.1 (CH), 125.2 (CH), 118.0 (CH), 108.6 (C), 83.1 (CH), 77.0 (CH), 51.4 (OCH_3), 33.9 (CH_2), 31.0 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 25.5 (CH_2), 24.9 (CH_2); HRMS *m/z* 356.1581 (M + Na), calcd for $C_{17}H_{23}N_3O_4Na$ 356.1586.

*Methyl 5-((4S,5S)-5-(2-Aminophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (**14aa**).* Prepared following the procedure **K** and purified by column chromatography using EtOAc/hexane (1:9) and isolated as a liquid; Yield: 81% (15.0 mg); $[\alpha]_D^{25}$ = −10.6° (*c* = 0.17, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3454 (NH_2), 3367 (NH_2), 2933, 1734 (C═O), 1618, 1499, 1460, 1436, 1378, 1305, 1228, 1168, 1089, 1036, 902, and 866 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (1H, dt, *J* = 7.5, 1.5 Hz), 7.02 (1H, dd, *J* = 7.5, 1.5 Hz), 6.71 (1H, dt, *J* = 7.5, 1.0 Hz), 6.65 (1H, dd, *J* = 8.0, 1.0 Hz), 4.57 (1H, d, *J* = 8.5 Hz), 4.29 (2H, br s, NH_2), 4.22−4.18 (1H, m), 3.64 (3H, s, OCH_3), 2.28 (2H, t, *J* = 7.0 Hz), 1.65−1.55 (5H, m), 1.54 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.40−1.35 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 174.0 (C, *C*═O), 145.9 (C), 129.3 (CH), 129.2 (CH), 119.6 (C), 118.1 (CH), 116.7 (CH), 108.4 (C), 83.4 (CH), 78.3 (CH), 51.4 (OCH_3), 33.9 (CH_2), 32.1 (CH_2), 27.3 (CH_3), 27.1 (CH_3), 25.8 (CH_2), 25.0 (CH_2); HRMS *m/z* 330.1681 (M + Na), calcd for $C_{17}H_{25}NO_4Na$ 330.1681.

*(3aS,13bS)-2,2-Dimethyl-4,5,6,7,9,13b-hexahydrobenzo[b][1,3]-dioxolo[4,5-d]azecin-8(3aH)-one (**15aa**).* Prepared following the procedure **L** and purified by column chromatography using EtOAc/hexane (1:8) and isolated as a liquid; Yield: 57% (9.4 mg); $[\alpha]_D^{25}$ = −5.0° (*c* = 0.14, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3452, 3370 (NH), 2983, 2926, 2855, 1708 (C═O), 1617, 1499, 1460, 1379, 1233, 1169, 1087, 1037, 889, and 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (1H, dt, *J* = 8.0, 1.6 Hz), 7.03 (1H, dd, *J* = 7.6, 1.2 Hz), 6.73 (1H, dt, *J* = 7.2, 0.8 Hz), 6.67 (1H, d, *J* = 8.0 Hz), 4.59 (1H, d, *J* = 8.8 Hz), 4.24−4.19 (1H, m), 2.32 (2H, t, *J* = 7.2 Hz), 1.67−1.56 (5H, m), 1.55 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.46−1.37 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 178.5 (C, *C*═O), 145.8 (C), 129.3 (CH), 129.2 (CH), 119.6 (C), 118.2 (CH), 116.8 (CH), 108.4 (C), 83.4 (CH), 78.3 (CH), 33.7 (CH_2), 32.0 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 25.7 (CH_2), 24.7 (CH_2); HRMS *m/z* 276.1594 (M + H), calcd for $C_{16}H_{22}NO_3$ 276.1599.

*(1S,2S)-1-(2-Azidophenyl)heptane-1,2,7-triol (**16aa**).* Prepared following the procedure **M** and purified by column chromatography using EtOAc/hexane (1:2) and isolated as a liquid; Yield: 69% (457.7 mg); $[\alpha]_D^{25}$ = +97.5° (*c* = 0.36, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3360 (OH), 2930, 2857, 2122 (N_3), 1713 (C═O), 1583, 1488, 1450, 1284, 1046, and 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 9.2 Hz), 7.34 (1H, dt, *J* = 7.6, 1.6 Hz), 7.18−7.14 (2H, m), 4.72 (1H, d, *J* = 5.6 Hz), 3.74−3.70 (1H, m), 3.59 (2H, t, *J* = 6.4 Hz), 3.22 (1H, br s, O*H*), 2.78 (1H, br s, O*H*), 1.94 (1H, br s, O*H*), 1.56−1.44 (4H, m), 1.39−1.24 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.0 (C), 132.6 (C), 128.9 (CH), 128.3 (CH), 125.0 (CH), 118.0 (CH), 74.8 (CH), 72.5 (CH), 62.7 (CH_2), 32.7 (CH_2), 32.4 (CH_2), 25.5 (CH_2), 25.4 (CH_2); HRMS *m/z* 288.1323 (M + Na), calcd for $C_{13}H_{19}N_3O_3$ 288.1324.

*5-((4S,5S)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-pentan-1-ol (**17aa**).* Prepared following the procedure **N** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as a liquid; Yield: 45% (185.5 mg); $[\alpha]_D^{25}$ = +100.3° (*c* = 0.28, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3370 (OH), 2935, 2125 (N_3), and 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (1H, dd, *J* = 7.6, 1.6 Hz), 7.35 (1H, dt, *J* = 7.6, 1.6 Hz), 7.19 (1H, dt, *J* = 7.6, 0.8 Hz), 7.16 (1H, dd, *J* = 8.0, 0.8 Hz), 4.94 (1H, d, *J* = 8.4 Hz), 3.77−3.72 (1H, m), 3.61 (2H, t, *J* = 6.8 Hz), 1.66−1.57 (4H, m), 1.56 (3H, s, CH_3), 1.49 (3H, s, CH_3),1.41−1.24 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.9 (C), 129.3 (CH), 129.2 (C), 128.2 (CH), 125.2 (CH), 118.0 (CH), 108.6 (C), 83.3 (CH), 77.0 (CH), 62.8 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 25.75 (CH_2), 25.72 (CH_2); HRMS *m/z* 328.1636 (M + Na), calcd for $C_{16}H_{23}N_3O_3Na$ 328.1637.

*5-((4S,5S)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-pentanal (**18aa**).* Prepared following the procedure **O** and purified by column chromatography using EtOAc/hexane (1:12) and isolated as a liquid; Yield: 74% (179.5 mg); $[\alpha]_D^{25}$ = +53.3° (*c* = 0.20, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 2929, 2858, 2123 (N_3), 1723 (C═O), 1585, 1489, 1453, 1370, 1292, 1236, 1164, 1100, 1050, 886, and 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.74 (1H, s, C*H*O), 7.54 (1H, d, *J* = 6.8 Hz), 7.35 (1H, t, *J* = 6.4 Hz), 7.21−7.15 (2H, m), 4.94 (1H, d, *J* = 8.0 Hz), 3.73 (1H, q, *J* = 8.4 Hz), 2.42 (2H, t, *J* = 6.4 Hz), 1.66−1.64 (4H, m), 1.55 (3H, s), 1.49 (3H, s),1.40−1.26 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 202.4 (CH, *C*HO), 137.8 (C), 129.3 (CH), 129.1 (C), 128.1 (CH), 125.2 (CH), 118.0 (CH), 108.6 (C), 83.1 (CH), 77.0 (CH), 43.7 (CH_2), 31.1 (CH_2), 27.4 (CH_3), 27.0 (CH_3), 25.5 (CH_2), 22.0 (CH_2); HRMS *m/z* 326.1469 (M + Na), calcd for $C_{16}H_{21}N_3O_3Na$ 326.1481.

*8-((4S,5S)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-1-yn-4-ol (**19aa**).* Prepared following the procedure **P** and purified by column chromatography using EtOAc/hexane (1:7) and isolated as a liquid; Yield: 63% (177.0 mg); $[\alpha]_D^{25}$ = +3.9° (*c* = 0.26, $CHCl_3$); IR (Neat): ν_{max} 3436 (OH), 3307, 2990, 2933, 2863, 2246, 2122 (N_3), 2084, 1584, 1492, 1454, 1372, 1299, 1230, 1169, 1103, 1046, and 884 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (1H, br d, *J* = 7.6 Hz), 7.35 (1H, br t, *J* = 7.6 Hz), 7.19 (1H, br t, *J* = 7.6 Hz), 7.16 (1H, br d, *J* = 8.0 Hz), 4.95 (1H, d, *J* = 8.0 Hz), 3.75−3.73 (2H, m), 2.42−2.26 (2H, m), 2.04 (1H, br s), 1.99 (1H, br s), 1.74−1.60 (3H, m), 1.56 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.52−1.26 (5H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.9 (C), 129.3 (CH), 129.2 (C), 128.2 (CH), 125.1 (CH), 118.1 (CH), 108.6 (C), 83.3 (CH), 80.9 (C), 77.0 (CH), 70.8 (CH), 69.7 (CH), 36.0 (CH_2), 31.3 (CH_2), 27.4 (CH_3), 27.3 (CH_2), 27.1 (CH_3), 25.8 (CH_2), 25.6 (CH_2); HRMS *m/z* 366.1787 (M + Na), calcd for $C_{19}H_{25}N_3O_3Na$ 366.1794.

*8-((4S,5S)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-octa-1,2-dien-4-one (**20aa**).* Prepared following the procedure **Q** and purified by column chromatography using EtOAc/hexane (1:17) and isolated as a liquid; Yield: 54% (37.0 mg); $[\alpha]_D^{25}$ = +10.3° (*c* = 0.37, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 2987, 2930, 2856, 2125 (N_3), 1933, 1681 (C═O), 1585, 1490, 1452, 1370, 1293, 1237, 1171, 1041, and 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (1H, dd, *J* = 7.6, 1.6 Hz), 7.34 (1H, dt, *J* = 7.6 1.6 Hz), 7.18 (1H, dt, *J* = 7.6, 0.8 Hz), 7.15 (1H, dd, *J* = 8.0, 0.8 Hz), 5.75 (1H, t, *J* = 6.8 Hz), 5.19 (2H, d, *J* = 6.4 Hz), 4.93 (1H, d, *J* = 8.8 Hz), 3.75−3.67 (1H, m), 2.58 (2H, t, *J* = 7.2 Hz), 1.66−1.56 (4H, m), 1.54 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.36−

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1.30 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 216.6 (C, HC═*C*═CH_2), 200.6 (C, *C*═O), 137.8 (C), 129.25 (CH), 129.18 (C), 128.1 (CH), 125.2 (CH),118.0 (CH), 108.6 (C), 96.6 (CH), 83.2 (CH), 79.3 (CH_2), 77.0 (CH), 38.9 (CH_2), 31.1 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 25.5 (CH_2), 24.5 (CH_2); HRMS *m*/*z* 364.1633 (M + Na), calcd for $C_{19}H_{23}N_3O_3Na$ 364.1637.

*Diethyl 1-(2-((S)-Hydroxy((S)-7-oxooxepan-2-yl)methyl)phenyl)-1H-1,2,3-triazole-4,5-dicarboxylate (**21aa**).* Prepared following the procedure **R** and purified by column chromatography using EtOAc/hexane (1:3) and isolated as a liquid; Yield: 55% (23.7 mg); $[\alpha]_D^{25}$ = +17.2° (*c* = 0.28, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3496 (OH), 2984, 2940, 2864, 1733 (C═O), 1558, 1498, 1444, 1376, 1348, 1285, 1254, 1226, 1189, 1087, 1016, and 771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (1H, br d, *J* = 6.8 Hz), 7.65 (1H, br t, *J* = 6.8 Hz), 7.51 (1H, dt, *J* = 7.6, 1.2 Hz), 7.31 (1H, br d, *J* = 7.6 Hz), 4.49 (2H, q, *J* = 6.8 Hz), 4.41 (1H, br d, *J* = 6.0 Hz), 4.31−4.23 (1H, m), 4.26 (2H, q, *J* = 6.8 Hz), 3.00 (1H, br s, OH), 2.67−2.62 (1H, m), 2.56−2.48 (1H, m), 1.89−1.86 (2H, m), 1.74−1.67 (2H, m), 1.61−1.49 (2H, m), 1.45 (3H, t, *J* = 7.2 Hz), 1.16 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 174.4 (C, *C*═O), 159.6 (C, *C*═O), 158.0 (C, *C*═O), 139.0 (C), 137.0 (C), 133.9 (C), 133.6 (C), 131.5 (CH), 129.2 (CH), 129.0 (CH), 127.5 (CH), 82.8 (CH), 72.3 (CH), 63.2 (CH_2), 62.0 (CH_2), 34.7 (CH_2), 30.9 (CH_2), 27.7 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 13.6 (CH_3); HRMS *m*/*z* 454.1585 (M + Na), calcd for $C_{21}H_{25}N_3O_7Na$ 454.1590.

*Diethyl 1-(2-((1S,2S)-1,2-Dihydroxy-7-methoxy-7-oxoheptyl)-phenyl)-1H-1,2,3-triazole-4,5-dicarboxylate (**22aa**).* Prepared following the procedure **S** and purified by column chromatography using EtOAc/hexane (1:2) and isolated as a liquid; Yield: 80% (37.0 mg); $[\alpha]_D^{25}$ = +23.0° (*c* = 0.17, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): ν_{max} 3481 (OH), 2982, 2941, 2864, 1731 (C═O), 1557, 1496, 1438, 1376, 1285, 1252, 1195, 1082, 1013, and 766 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71 (1H, dd, *J* = 7.6, 1.2 Hz), 7.63 (1H, dt, *J* = 7.6, 0.8 Hz), 7.47 (1H, dt, *J* = 7.6, 1.2 Hz), 7.27 (1H, dd, *J* = 7.6, 0.8 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 4.34−4.22 (2H, m), 4.10 (1H, d, *J* = 5.6 Hz), 3.79−3.72 (1H, m), 3.63 (3H, s, O*CH*$_3$), 3.27 (1H, br s), 2.67 (1H, br s), 2.23 (2H, dt, *J* = 7.6, 1.2 Hz), 1.59−1.48 (2H, m), 1.45 (3H, t, *J* = 7.2 Hz), 1.41−1.30 (4H, m), 1.26 (3H, t, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 174.1 (C, *C*═O), 159.6 (C, *C*═O), 158.6 (C, *C*═O), 138.91 (C), 138.89 (C), 133.5 (C), 133.4 (C), 131.6 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 74.0 (CH), 72.3 (CH), 63.4 (CH_2), 62.0 (CH_2), 51.4 (CH_3), 33.8 (CH_2), 32.1 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 14.2 (CH_3), 13.6 (CH_3); HRMS *m*/*z* 486.1847 (M + Na), calcd for $C_{22}H_{29}N_3O_8Na$ 486.1852.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02896.

Characterization data (including ^{1}H NMR spectra) for products and additional schemes and figures (PDF)
General methods for HPLC analysis and HPLC spectra (PDF)
^{1}H and ^{13}C NMR spectra (PDF)
X-ray crystallographic data for (−)-**5ca** (CIF)
X-ray crystallographic data for (−)-**5ac** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ramsc@uohyd.ac.in and ramchary.db@gmail.com.

Notes

The authors declare no competing financial interest.

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