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不对称有机催化构筑二环己内酰胺类化合物

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摘要 设计了一例 *α*,*β*-不饱和烯醛与含有双亲核活性中心的 *α*-酮酰胺不对称有机催化高选择性的 Michael-hemiamination-hemiacetalization 串联反应, 并以高收率(up to 97%)、优异的对映选择性和非对映选择性(up to＞99% *ee*, ＞20∶1 *dr*)获得一系列具有两个顺式手性中心的二环己内酰胺化合物.

关键词 不对称合成; Michael-hemiaminalization-hemiacetalization 反应; 二环己内酰胺

Asymmetric Organocatalytic Construction of Functionalized Bicyclic Lactams

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Abstract A novel enantioselective organocatalytic cascade Michael-hemiaminalization-hemiacetalization reaction of *α*,*β*-unsaturated aldehydes with *α*-ketoamides as binucleophiles has been developed. A series of chiral functionalized bicyclic lactams with two *cis* contiguous stereogenic centers have been synthesized in up to 97% yield with up to ＞20∶1 *dr* and up to ＞99% *ee*.

Keywords asymmetric synthesis; Michael-hemiaminalization-hemiacetalization reaction; bicyclic lactam

不对称有机催化串联反应[1]在不对称合成领域正展示着迷人的魅力, 它为快速构建大量手性杂环化合物和多样性的分子结构提供了一种高效、原子经济性的合成方法[2]. 为了保证多步串联反应过程能够顺利进行, 反应底物通常需要具有多个潜在的反应位点, 并且能够在反应中进行选择性地活化和控制. 1,2-二羰基化合物由于相邻两个羰基的互相影响, 这类化合物通常含有两个亲核反应中心和两个亲电活性位点[3], 在这一背景下, 1,2-二羰基化合物引起了人们极大的兴趣[4]. 在手性仲胺催化下, Dondoni[5], Landais[6]和 Li[7]等报道了采用丙酮酸酯或 *α*-酮酰胺作为亲核试剂合成了一系列丁内酯类化合物的多种方法. Rueping[8]和 Zhao[9]两个课题组也分别以 1,2-二酮类化合物作为亲核试剂, 经过不对称 Michael-aldol 串联反应合成了一类手性二胺化合物. 最近, Alexakis 及其合作者[10]发展了一类 3-卤代-1,2-二酮化合物通过与 *α*,*β*-不饱和醛发生 Michael-aldol 串联反应, 得到了一类含有两个全取代手性中心的环戊酮类化合物的方法. 以上关于 1,2-二羰基化合物参与的有机不对称串联反应均是基于 1,2-二羰基化合物潜在的亲核性来实现其对亲电试剂的进攻, 进而引发串联反应得到环状产物.

最近, *α*-酮酰胺由于其具有双亲核活性中心在有机不对称催化领域引起了广泛的关注[11]. 理论上来说, 在串联反应中通过对两个活性位点的选择性控制, 可以有序实现 C—C 和 C—N 键的构建, 得到一系列五元环、六元环或七元环的杂环产物. 2014 年, Bonne 和 Rodriguez 小组[11c]报道了一例二苯基脯氨醇硅氧醚催化剂催化合成反式二环己内酰胺化合物的反应. 基于以上事实的分析和总结, 发展高效、高选择性的策略来合成不同构型的二环己内酰胺衍生物仍然具有一定的意义.

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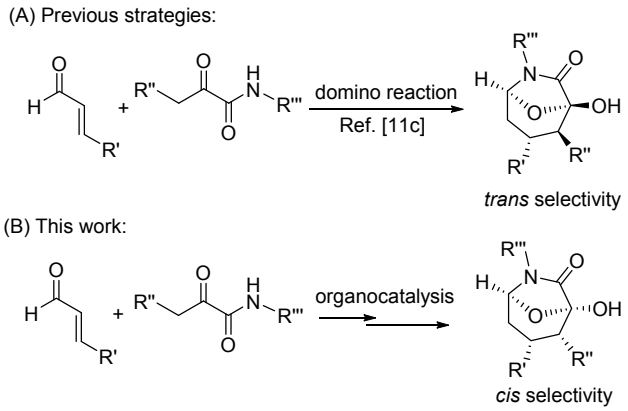
在最近十几年中，我们课题组[12]一直致力于有机小分子不对称催化合成手性化合物的反应研究，在2016年我们[12e]发展了α-酮酰胺、肉桂醛和硝基烯烃三组分“一锅法”反应合成了一类具有7个手性中心的二环类化合物. 因此在此前工作的基础上，我们尝试发展一种有机小分子催化 α,β-不饱和醛与 α-酮酰胺的Michael-hemiaminalization-hemiacetalization反应[13]合成亚胺糖类[14]和许多天然产物[15]都含有的顺式二环己内酰胺化合物(Scheme 1). 该方法存在一个较大的困难挑战，那就是如何设计一个合适的催化体系，该催化体系要能在很好地减少 α-酮酰胺自缩合的同时还能增强羰基相邻的亚甲基部分和酰胺部分的亲核性以及该二部分基团进行反应的连续性.



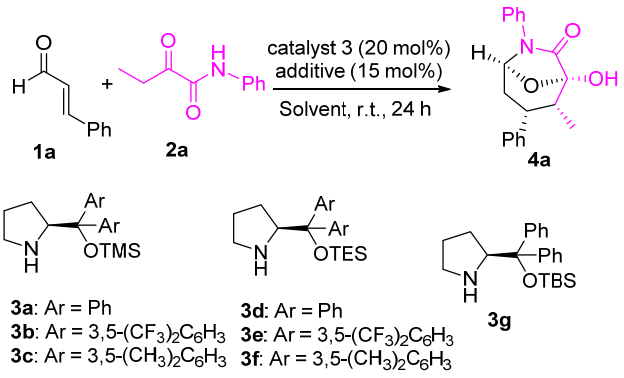
图式 1 多功能化二环己内酰胺的高选择性合成方法
Scheme 1 Enantioselective synthesis of functionalized bicyclic lactams

1 结果与讨论

1.1 反应条件的优化

首先选用肉桂醛(**1a**)与α-酮酰胺**2a**为底物，甲苯为溶剂，二苯基脯氨醇硅氧醚**3a**为手性催化剂，苯甲酸为添加剂，在反应 24 h 之后，几乎没有得到任何产物(表1, Entry 1). 但是，当采用三乙胺代替苯甲酸作为添加剂时，反应可以得到79%的收率和2.8∶1 *dr* 值以及对映体过量值分别为94% *ee*, 97% *ee* 的二环己内酰胺**4a**(表1, Entry 2). 接下来，通过对催化剂(表1, Entries 4～9)、溶剂(表 1, Entries 10～13)和碱性添加剂(表 1, Entries 14～19)的筛选对反应条件进行系统地优化，当反应采用手性催化剂**3g**和三乙胺为添加剂以及甲苯为溶剂时，手性二环己内酰胺产物**4a**能够达到85%的收率和3.0∶1 *dr* 值以及分别为99% *ee*, 99% *ee* 的对映选择性. 进一步研究发现：反应温度对产物的立体构型有较大的影响，当反应温度为 0 ℃时，产物 **4a** 的非对映选择性从3.0∶1提高到5.7∶1 (表1, Entry 20 vs Entry 9).

表 1 反应条件的优化 [a]
Table 1 Optimization of reaction conditions



Entry	Cat.	Additive	Solvent	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	**3a**	$PhCO_2H$	PhMe	Trace	—	—
2	**3a**	TEA	PhMe	79	2.8∶1	94 (97)
3	—	TEA	PhMe	—	—	—
4	**3b**	TEA	PhMe	68	11∶1	91 (99)
5	**3c**	TEA	PhMe	94	2.6∶1	88 (96)
6	**3d**	TEA	PhMe	81	2.5∶1	95 (95)
7	**3e**	TEA	PhMe	76	3.2∶1	91 (90)
8	**3f**	TEA	PhMe	93	2.8∶1	93 (96)
9	**3g**	TEA	PhMe	85	3.0∶1	99 (99)
10	**3g**	TEA	$PhCF_3$	99	1.5∶1	98 (98)
11	**3g**	TEA	DCE	98	1.3∶1	95 (96)
12	**3g**	TEA	AcOEt	75	3.1∶1	82 (99)
13	**3g**	TEA	$(i\text{-Pr})_2O$	80	4.7∶1	66 (99)
14	**3g**	DIPEA	PhMe	77	1.4∶1	96 (99)
15	**3g**	DABCO	PhMe	73	1.0∶1	97 (99)
16	**3g**	DBU	PhMe	56	1.7∶1	87 (80)
17	**3g**	DMAP	PhMe	95	1.1∶1	96 (99)
18	**3g**	K_2CO_3	PhMe	33	1.8∶1	86 (91)
19	**3g**	$Cu(OAc)_2$	PhMe	69	3.5∶1	98 (99)
20[e]	**3g**	TEA	PhMe	80	5.7∶1	99 (98)

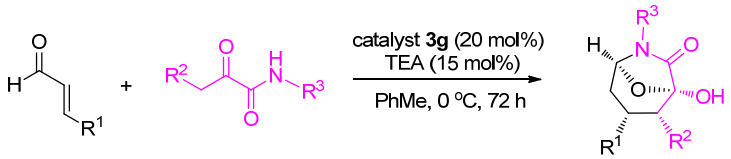
[a] Unless otherwise noted, the reactions were conducted in solvent (0.5 mL) using cinnamaldehyde **1a** (0.24 mmol) and 2-oxo-*N*-phenylbutanamide (**2a**, 0.2 mmol) in the presence of 20 mol% catalyst **3** and 20 mol% additive at room temperature with vigorous stirring. [b] Yield of isolated product **4a** after column chromatography. [c] The *dr* of **4a** was determined by ^{1}H NMR. [d] The *ee* values of **4a** were determined by chiral HPLC analysis on OD-H, and values of *ee* for the smaller isomers are given in parentheses. [e] The reaction was carried out at 0 ℃ for 72 h.

1.2 底物拓展

以最优的催化反应条件(表 1, Entry 20)，我们系统考察了各种芳香族的不饱和烯醛和脂肪链的不饱和醛在催化体系中的普适性(表2). 如表2所示，该催化体系对不同结构的 α,β-不饱和烯醛具有很好的适用性. 芳环上不管是有供电子还是吸电子取代基时，反应都能取得较好的收率、优异的对映选择性以及较好的非对映选择性(表 2, Entries 1～12). 脂肪链的不饱和烯醛也能适用于这一体系，当以巴豆醛(**1m**)为底物时，反应产物 **4m** 也能取得 47%的收率和＞20∶1 *dr* 值以及分别为 98%

表 2 反应底物的普适性 [a]

Table 2 Scope of the cascade reaction



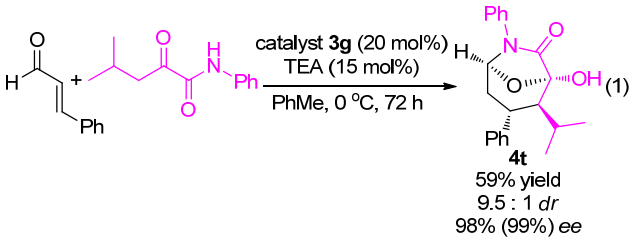
Entry	R^1	R^2	R^3	4	Yield[b]/%	*dr*[c]	*ee*[d]/%
1	Ph	Me	Ph	**4a**	80	5.7∶1	99 (98)
2	2-ClC_6H_4	Me	Ph	**4b**	94	2.1∶1	99 (99)
3	2-BrC_6H_4	Me	Ph	**4c**	78	1.7∶1	>99 (>99)
4	2-$MeOC_6H_4$	Me	Ph	**4d**	97	4.4∶1	92 (91)
5	3-FC_6H_4	Me	Ph	**4e**	89	5.1∶1	98 (96)
6	3-ClC_6H_4	Me	Ph	**4f**	95	4.6∶1	>99 (>99)
7	3-$MeOC_6H_4$	Me	Ph	**4g**	95	4.0∶1	98 (95)
8	4-FC_6H_4	Me	Ph	**4h**	74	5.3∶1	95 (99)
9	4-ClC_6H_4	Me	Ph	**4i**	85	4.3∶1	>99 (96)
10	4-BrC_6H_4	Me	Ph	**4j**	79	3.7∶1	99 (96)
11	4-$MeOC_6H_4$	Me	Ph	**4k**	85	3.0∶1	90 (92)
12	4-MeC_6H_4	Me	Ph	**4l**	60	3.6∶1	99 (98)
13	Me	Me	Ph	**4m**	47	>20∶1	98 (>99)
14	Propyl	Me	Ph	**4n**	93	7.7∶1	89 (79)
15	*i*-Propyl	Me	Ph	**4o**	67	7.0∶1	98 (87)
16	Ph	Me	$CH_2C_6H_5$	**4p**	58	1.6∶1	99 (79)
17	Ph	Me	3,5-$(CF_3)_2C_6H_3$	**4q**	95	49∶1	62 (—)
18	Ph	Me	3,5-$(MeO)_2C_6H_3$	**4r**	90	1.3∶1	92 (89)
19	Ph	Et	Ph	**4s**	56	1.3∶1	99 (98)

[a] Unless otherwise noted, the reactions were conducted in toluene (0.5 mL) using *α*,*β*-unsaturated aldehydes **1** (0.24 mmol) and *α*-ketoamides **2** (0.2 mmol) in the presence of 20 mol% catalyst **3g** and 20 mol% TEA in toluene at 0 ℃ with vigorous stirring. [b] Yield of isolated product **4** after column chromatography. [c] The *dr* of **4** were determined by ^{1}H NMR. [d] The *ee* values of **4** were determined by chiral HPLC analysis, and the ee values of the smaller isomers are given in parentheses.

ee, 99% *ee* 的对映选择性(Entry 14). 当不饱和醛 R^1 是丙基以及异丙基时, 反应产物 **4n** 和 **4o** 分别可以得到 93% 和 67%的收率, 产物的立体选择性也很好(Entries 14, 15, 7.7∶1 *dr*, 89% *ee*, 79% *ee* 和 7.0∶1 *dr*, 98% *ee*, 87% *ee*). 对比芳香族不饱和烯醛的非对映选择性, 我们发现脂肪族烯醛参与反应所得到的产物具有更高的非对映选择性, 在这样的反应体系中, 脂肪族烯醛的链状结构要比芳香族烯醛的平面结构更加适合. 另外, *α*-酮酰胺 **2p**～**2r** 也被应用于这一反应体系, 相应的二环己内酰胺产物均能顺利地通过该反应体系来获得, 经反应可以得到最高为 95%的收率和 49∶1 *dr* 值以及 99% *ee* 的对映选择性产物(Entries 16～18).

需要特别指出的是当 R^2 基团为乙基时, 经反应仍然可以得到收率为 56%的顺式结构产物 **4r**(表 2, Entry 19); 但当 R^2 基团为较大的基团异丙基时, 经反应得到 59%的收率, 9.5∶1 *dr* 值, 和分别为 98% *ee*、99% *ee* 对映选择性的反式结构产物 **4t** (Eq. 1). 笔者分析认为出现这种情况的原因可能是 R^2 基团和催化剂中硅烷基的空间位阻共同影响了反应催化过渡态而导致的.

产物 **4a**～**4s** 的绝对构型为(1*R*,2*R*,3*R*,5*S*), 通过对产物 **4f** 进行单晶衍射得到了验证(图 1)[16].



(1)

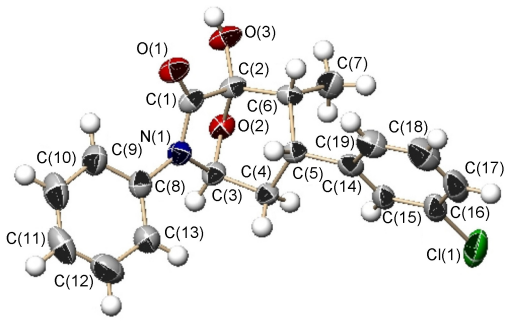


图 1 化合物 **4f** 的分子结构图

Figure 1 X-ray crystal structure of the adduct **4f**

2 结论

报道了一种高效的手性仲胺二苯基脯氨醇硅氧醚催化剂催化的不对称 Michael-hemiaminalizationhemi-

acetalization 反应来合成含有两个顺式手性中心的多功能二环己内酰胺的方法. 反应以肉桂醛(**1a**)与 α-酮酰胺 **2a** 为底物, 甲苯为溶剂, 三乙胺为碱性添加剂, 脂肪链以及芳香环取代的底物在该体系下可以得到最高 97% 的收率和 99% *ee* 值的对映选择性以及＞20∶1 的非对映选择性. 该反应具有反应条件温和、反应选择性高、操作简单等优点.

3 实验部分

3.1 仪器与试剂

^{1}H NMR 和 ^{13}C NMR 均在德国 Bruker 公司 500 MHz 核磁共振仪上测定, 溶剂 $CDCl_3$, 内标 TMS. 高分辨质谱数据的测定使用 Agilent 1200 液相色谱-6210 飞行时间质谱仪测定; 对映选择性使用 JASCO LC-2000 手性液相和大赛璐手性色谱柱测定. 实验所用药品和试剂均为市售的分析纯或化学纯, 除特别说明外, 未经进一步处理.

3.2 实验方法

向有搅拌磁子的 Schlenk 反应管(10 mL)中一次加入烯醛 **1** (0.24 mmol)、α-酮酰胺 **2** (0.2 mmol)、(2*S*)-2-[二苯基(三丁基硅烷氧基)甲基]吡咯烷(20 mol%)、三乙胺(20 mol%)和甲苯(0.5 mL). 该反应体系在 0 ℃下反应 72 h. 待反应结束后, 通过旋转蒸发仪除去有机溶剂, 残留物通过柱层析(石油醚和乙酸酯混合液为洗脱剂)方法分离出目标产物 **4**, 干燥、称量质量确定收率. 所有产物均经过核磁和高分辨质谱确认.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-2-二甲基-3,6-二苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4a**): 产率 80%, 99%, 98% *ee*, 5.7∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (*V*∶*V*＝80∶20); Flow: 1.0 mL/min; UV *λ*＝276 nm; t^1_{minor}＝11.493 min, t^1_{major}＝8.373 min, t^2_{minor}＝13.692 min, t^2_{major}＝9.013 min. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.60～7.58 (m, 2H), 7.40～7.36 (m, 2H), 7.33～7.30 (m, 2H), 7.25～7.14 (m, 4H), 5.95 (s, 1H), 4.58 (s, 1H), 3.30～3.25 (m, 1H), 2.48～2.36 (m, 2H), 2.05～2.01 (m, 1H), 0.87 (d, *J*＝6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.3, 139.9, 135.8, 129.5 (2C), 128.6 (2C), 127.6 (2C), 126.8, 125.4, 118.7 (2C), 101.8, 85.8, 38.2, 38.1, 25.9, 6.8; HRMS (ESI) calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$ 310.1443, found 310.1432.

(1*R*,2*R*,3*R*,5*S*)-3-(2-氯代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4b**): 产率 94%, 99%, 99% *ee*, 2.1∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (*V*∶*V*＝90∶10); Flow: 1.0 mL/min; UV *λ*＝268 nm; t^1_{minor}＝24.052 min, t^1_{major}＝15.732 min, t^2_{minor}＝29.771 min, t^2_{major}＝17.772 min. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.56～7.54 (m, 2H), 7.36～7.32 (m, 3H), 7.24～7.16 (m, 4H), 5.92 (s, 1H), 5.27 (s, 1H), 3.72～3.70 (m, 1H), 2.68～2.62 (m, 1H), 2.50～2.45 (m, 1H), 1.87～1.83 (m, 1H), 0.87 (d, *J*＝6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.6, 136.9, 135.6, 134.23, 130.0, 129.4 (2C), 128.9, 128.1, 126.6, 125.5, 119.2 (2C), 102.0, 85.7, 35.5, 34.9, 25.8, 7.1; HRMS (ESI) calcd for $C_{19}H_{19}ClNO_3$ $[M+H]^+$ 344.1053, found 344.1058.

(1*R*,2*R*,3*R*,5*S*)-3-(2-溴代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4c**): 产率 78%, ＞99%, ＞99% *ee*, 1.7∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (*V*∶*V*＝90∶10); Flow: 1.0 mL/min; UV *λ*＝272 nm; t^1_{minor}＝23.687 min, t^1_{major}＝15.466 min, t^2_{minor}＝31.251 min, t^2_{major}＝17.292 min. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.59～7.55 (m, 3H), 7.40～7.36 (m, 2H), 7.30～7.29 (m, 1H), 7.21～7.17 (m, 2H), 7.13～7.09 (m, 1H), 5.94 (t, *J*＝1.8 Hz, 1H), 4.57 (s 1H), 3.73～3.68 (m, 1H), 2.70～2.64 (m, 1H), 2.50～2.43 (m, 1H), 1.89～1.85 (m, 1H), 0.87 (d, *J*＝7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.4, 138.4, 135.7, 133.4, 129.5 (2C), 129.2, 128.4, 127.2, 125.6, 125.1, 119.3 (2C), 101.8, 85.9, 38.2, 34.9, 26.0, 7.0; HRMS (ESI) calcd for $C_{19}H_{19}BrNO_3$ $[M+H]^+$ 388.0548, found 388.0552.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-3-(2-甲氧基苯基)-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4d**): 产率 97%, 93%, 90% *ee*, 3.0∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (*V*∶*V*＝90∶10); Flow: 1.0 mL/min; UV *λ*＝272 nm; t^1_{minor}＝29.531 min, t^1_{major}＝36.797 min, t^2_{minor}＝41.090 min, t^2_{major}＝44.969 min. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.57～7.56 (m, 2H), 7.36～7.33 (m, 2H), 7.24～7.20 (m, 1H), 7.17～7.10 (m, 2H), 6.94～6.91 (m, 1H), 6.84～6.82 (m, 1H), 5.90 (s, 1H), 4.95 (s, 1H), 3.77 (s, 3H), 3.68～3.63 (m, 1H), 2.67～2.62 (m, 1H), 2.51～2.46 (m, 1H), 1.88～1.83 (m, 1H), 0.83 (d, *J*＝7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.8, 157.1, 136.0 129.3 (2C), 128.1, 127.7, 125.2, 120.1, 118.9 (2C), 110.2, 102.2, 86.0, 55.2, 35.2, 32.2, 29.7, 25.8, 7.2; HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1549, found 340.1544.

(1*R*,2*R*,3*R*,5*S*)-3-(3-氟代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4e**): 产率 89%, 98%, 96% *ee*, 5.1∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (*V*∶*V*＝80∶20); Flow: 1.0 mL/min; UV *λ*＝268 nm; t^1_{minor}＝13.372 min, t^1_{major}＝9.493 min, t^2_{minor}＝16.745 min, t^2_{major}＝11.279 min. ^{1}H NMR (500

MHz, $CDCl_3$) δ: 7.56～7.54 (m, 2H), 7.36～7.33 (m, 2H), 7.30～7.25 (m, 1H), 7.18～7.15 (m, 1H), 6.94～6.91 (m, 2H), 6.87～6.85 (m, 1H), 5.92 (s, 1H), 5.28 (s, 1H), 3.27～3.22 (m, 1H), 2.42～2.35 (m, 2H), 2.03～1.99 (m, 1H), 0.88 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 163.0 (d, $^1J_{C\text{-}F}$=244.6 Hz), 142.7 (d, $^3J_{C\text{-}F}$=6.9 Hz), 135.7, 123.0 (d, $^3J_{C\text{-}F}$=8.3 Hz), 129.4 (2C), 125.4, 123.3, 118.6 (2C), 114.6 (d, $^2J_{C\text{-}F}$=21.8 Hz), 113.7 (d, $^2J_{C\text{-}F}$=20.8 Hz), 102.0, 85.5, 37.9 (d, $^4J_{C\text{-}F}$=9.9 Hz), 29.7, 25.8, 6.8; HRMS (ESI) calcd for $C_{19}H_{19}FNO_3$ $[M+H]^+$ 328.1349, found 328.1353.

(1*R*,2*R*,3*R*,5*S*)-3-(3-氯代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4f**): 产率 95%, ＞99%, 90% *ee*, 4.6∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (V∶V＝80∶20); Flow: 1.0 mL/min; UV＝232 nm; t^1_{minor}＝14.372 min, t^1_{major}＝9.453 min, t^2_{minor}＝17.252 min, t^2_{major}＝10.773 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55～7.54 (m, 2H), 7.37～7.34 (m, 2H), 7.25～7.14 (m, 4H), 7.04～7.03 (m, 1H), 5.92 (s, 1H), 5.00 (s, 1H), 3.25～3.21 (m, 1H), 2.41～2.36 (m, 2H), 2.02～1.98 (m, 1H), 0.88 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5, 142.1, 135.7, 134.5, 129.8, 129.4 (2C), 127.7, 127.0, 125.8, 125.4, 118.6 (2C), 101.9, 85.4, 37.9 (2C), 25.7, 6.8; HRMS (ESI) calcd for $C_{19}H_{19}ClNO_3$ $[M+H]^+$ 344.1053, found 344.1065.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-3-(3-甲氧代苯基)-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4g**): 产率 95%, 98%, 95% *ee*, 4.0∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ=280 nm; t^1_{minor}=31.282 min, t^1_{major}=36.427 min, t^2_{minor}=50.422 min, t^2_{major}=60.592 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57～7.56 (m, 2H), 7.37～7.34 (m, 2H), 7.28～7.17 (m, 2H), 6.78～6.74 (m, 2H), 6.70～6.69 (m, 1H), 5.98 (s, 1H), 4.94 (s, 1H), 3.79 (s, 3H), 3.26～3.210 (m, 1H), 2.43～2.37 (m, 2H), 2.03～1.99 (m, 1H), 0.89 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 159.8, 141.6, 135.8, 129.4, 129.4 (2C), 125.4, 119.9, 119.9, 118.7 (2C), 113.6, 111.9, 102.0, 85.7, 55.2, 38.1, 25.9, 6.8; HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1549, found 340.1536.

(1*R*,2*R*,3*R*,5*S*)-3-(4-氟代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4h**): 产率 74%, 95%, 99% *ee*, 5.3∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ＝260 nm; t^1_{minor}＝12.306 min, t^1_{major}＝8.946 min, t^2_{minor}＝14.879 min, t^2_{major}＝10.346 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56～7.54 (m, 2H), 7.38～7.33 (m, 2H), 7.18～7.16 (m, 3H), 7.01～6.97 (m, 2H), 5.87 (s, 1H), 5.81 (s, 1H), 2.61～2.52 (m, 1H), 2.31～2.25 (m, 1H), 2.18～2.11 (m, 2H), 0.96 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 161.8 (d, $^1J_{C\text{-}F}$ ＝ 243.6 Hz), 137.3 (d, $^4J_{C\text{-}F}$=3.1Hz), 135.8, 129.4 (d, $^3J_{C\text{-}F}$=6.4 Hz, 2C), 129.39, 125.38 (2C), 118.8 (2C), 115.5 (d, $^2J_{C\text{-}F}$=21.0 Hz, 2C), 102.4, 85.6, 43.5, 41.8, 35.4, 12.2; HRMS (ESI) calcd for $C_{19}H_{19}FNO_3$ $[M+H]^+$ 328.1349, found 328.1355.

(1*R*,2*R*,3*R*,5*S*)-3-(4-氯代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4i**): 产率 85%, ＞99%, 96% *ee*, 4.3∶1 *dr*. HPLC on Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V＝80∶20); Flow: 1.0 mL/min; UV＝272 nm; t^1_{minor}＝28.750 min, t^1_{major}＝32.402 min, t^2_{minor}=60.178 min, t^2_{major}=68.269 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.545～7.527 (m, 2H), 7.363～7.275 (m, 4H), 7.17～7.12 (m, 1H), 7.08～7.01 (m, 2H), 5.90 (s, 1H), 5.59 (s, 1H), 3.23～3.18 (m, 1H), 2.40～2.33 (m, 2H), 1.99～1.95 (m, 1H), 0.86 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 138.5, 135.6, 132.5, 129.4 (2C), 129.0 (2C), 128.6 (2C), 125.4, 118.6 (2C), 102.1, 85.4, 37.9, 37.6, 25.8, 6.8; HRMS (ESI) calcd for $C_{19}H_{18}ClNNaO_3$ $[M+Na]^+$ 366.0873, found 366.0878.

(1*R*,2*R*,3*R*,5*S*)-3-(4-溴代苯基)-1-羟基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4j**): 产率 79%, 99%, 96% *ee*, 3.7∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ＝272 nm; t^1_{minor}＝21.192 min, t^1_{major}＝33.281 min, t^2_{minor}=78.412 min, t^2_{major}=63.591 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.58～7.56 (m, 2H), 7.45～7.43 (m, 2H), 7.41～7.36 (m, 2H), 7.23～7.14 (m, 1H), 7.03 (d, J=8.0 Hz, 2H), 5.93 (s, 1H), 3.23～3.19 (m, 1H), 2.38～2.34 (m, 2H), 2.02～1.98 (m, 1H), 0.86 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4, 138.9, 135.7, 131.6 (2C), 129.5 (2C), 129.3 (2C), 125.5, 120.7, 118.6 (2C), 101.8, 85.6, 37.9, 37.7, 25.8, 6.7; HRMS (ESI) calcd for $C_{19}H_{19}BrNO_3$ $[M+H]^+$ 388.0548, found 388.0545.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-3-(4-甲氧基苯基)-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4k**): 产率 85%, 90%, 92% *ee*, 3.0∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ＝280 nm; t^1_{minor}＝15.439 min, t^1_{major}＝9.893 min,

t^2_{minor}=17.732 min, t^2_{major}=11.333 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56～7.54 (m, 2H), 7.37～7.34 (m, 2H), 7.19～7.16 (m, 1H), 7.11 (d, J=4.5 Hz, 2H), 6.85 (d, J=4.2 Hz, 2H), 5.81 (d, J=4.7 Hz, 1H), 5.66 (s, 1H), 3.79 (s, 3H), 2.55～2.50 (m, 1H), 2.30～3.23 (m, 1H), 2.13～2.12 (m, 2H), 0.96 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 158.5, 135.9, 133.7, 129.4 (2C), 128.9 (2C), 125.3, 118.8 (2C), 114.1 (2C), 102.4, 85.7, 55.3, 43.3, 41.9, 35.467, 12.2; HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1549, found 340.1544.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-2-甲基-6-苯基-3-(4-甲苯基)-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4l**): 产率 60%, 99%, 98% *ee*, 3.6∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/EtOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ=260 nm; t^1_{minor}=28.616 min, t^1_{major}=29.629 min, t^2_{minor}=38.560 min, t^2_{major}=43.318 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57～7.56 (m, 2H), 7.40～7.36 (m, 2H), 7.21～7.18 (m, 1H), 7.13～7.08 (m, 4H), 5.85～5.82 (m, 1H), 5.09 (s, 1H), 2.58～2.53 (m, 1H), 2.33～2.30 (m, 4H), 2.16～2.13 (m, 2H), 0.96 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.9, 138.6, 136.6, 136.0, 129.4 (2C), 129.9 (2C), 127.9 (2C), 125.3, 118.8 (2C), 102.3, 85.9, 43.8, 41.7, 35.5, 21.0, 12.2; HRMS (ESI) calcd for $C_{20}H_{21}NNaO_3$ $[M+Na]^+$ 346.1419, found 346.1417.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-2,3-二甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4m**): 产率 47%, 98%, 99% *ee*, 20∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=90∶10); Flow: 1.0 mL/min; UV λ=236 nm; t^1_{minor}=37.010 min, t^1_{major}=34.398 min, t^2_{minor}=40.010 min, t^2_{major}=28.585 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.72～7.70 (m, 2H), 7.55 (s, 1H), 7.44～7.40 (m, 2H), 7.19～7.16 (m, 1H), 5.99 (s, 1H), 1.79～1.72 (m, 2H), 1.67～1.63 (m, 1H), 1.54～1.48 (m, 1H), 0.92 (d, J=6.5 Hz, 3H), 0.83 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5, 136.4, 129.3 (2C), 124.4, 118.1 (2C), 101.5, 84.2, 36.3, 29.3, 26.5, 17.0, 5.7; HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$ 248.2897, found 248.2889.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-2-甲基-6-苯基-3-丙基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4n**): 产率 93%, 89%, 79% *ee*, 7.7∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ=276 nm; t^1_{minor}=9.346 min, t^1_{major}=6.853 min, t^2_{minor}=10.746 min, t^2_{major}=8.239 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50～7.48 (m, 2H), 7.34～7.31 (m, 2H), 7.16～7.13 (m, 1H), 5.72 (s, 1H), 4.99 (s, 1H), 2.11～2.06 (m, 1H), 1.85～1.81 (m, 1H), 1.74～1.70 (m, 1H), 1.66～1.61 (m, 1H), 1.33～1.12 (m, 4H), 1.07 (d, J=7.0 Hz, 3H) 0.84 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 135.9, 129.3 (2C), 125.1, 118.7 (2C), 102.3, 85.9, 35.3, 33.9, 32.1, 28.5, 19.6, 14.0, 5.6; HRMS (ESI) calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.16, found 276.1599.

(1*R*,2*R*,3*R*,5*S*)-1-羟基-3-异丙基-2-甲基-6-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4o**): 产率 67%, 98%, 87% *ee*, 7.0∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ=272 nm; t^1_{minor}=9.866 min, t^1_{major}=6.826 min, t^2_{minor}=11.106 min. t^2_{major}=12.332 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50～7.48 (m, 2H), 7.36～7.33 (m, 2H), 7.18～7.15 (m, 1H), 5.74 (s, 1H), 4.86 (s, 1H), 2.21～2.17 (m, 1H), 1.86～1.83 (m, 1H), 1.64～1.55 (m, 2H), 1.35～1.31 (m, 1H), 1.09 (d, J=6.5 Hz, 3H), 0.87 (d, J=6.5 Hz, 3H (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 135.8, 129.3 (2C), 125.2, 118.7 (2C), 102.3, 85.9, 39.8, 34.4, 28.4, 26.6, 20.7, 19.8, 5.8; HRMS (ESI) calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, found 276.1610.

(1*R*,2*R*,3*R*,5*S*)-6-苄基-1-羟基-2-甲基-3-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4p**): 产率 58%, 99%, 79% *ee*, 1.6∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ=220 nm; t^1_{minor}=13.426 min, t^1_{major}=10.426 min, t^2_{minor}=23.318 min, t^2_{major}=26.385 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36～7.12 (m, 10H), 5.24 (s, 1H), 4.91 (d, J=15 Hz, 1H), 4.37 (s, 1H), 4.13 (d, J=15 Hz, 1H), 3.15～3.11 (m, 1H), 2.32～2.30 (m, 1H), 2.26～2.20 (m, 1H), 1.62～1.58 (m, 1H), 0.81 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 140.0, 134.5, 129.0 (2C), 128.5 (2C), 128.3, 128.2 (2C), 127.7 (2C), 126.7, 101.4, 84.4, 44.8, 38.4, 38.3, 25.3, 6.6; HRMS (ESI) calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$ 324.1600, found 324.1602.

(1*R*,2*R*,3*R*,5*S*)-6-(3,5-二(三氟甲基)苯基)-1-羟基-2-甲基-3-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4q**): 产率 95%, 62% *ee*, 49∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=95∶5); Flow: 1.0 mL/min; UV λ=296 nm; t^1_{minor}=21.465 min, t^1_{major}=8.333 min, t^2_{minor}=13.599 min, t^2_{major}=9.866 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 8.03 (s, 1H), 7.67 (s, 1H), 7.62 (s, 1H), 7.35～7.32 (m, 2H), 7.28～7.26 (m, 1H), 7.23～7.21 (m, 2H), 5.97 (s, 1H), 5.47 (s, 1H), 2.56～2.48 (m, 1H), 2.41～2.37 (m, 1H), 2.33～2.27 (m, 1H),

2.21～2.16 (m, 1H), 0.97 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.0, 140.8, 137.3, 133.0 (m, 2C), 128.8 (2C), 127.9 (2C), 127.4, 122.8 (m, 2C), 118.3 (m), 117.2 (m, 2C), 102.5, 85.5, 44.0, 41.5, 34.9, 12.0; HRMS (ESI) calcd for $C_{21}H_{18}F_6NO_3$ $[M+H]^+$ 444.1034, found 444.1031.

(1*R*,2*R*,3*R*,5*S*)-6-(3,5-二甲氧基苯基)-1-羟基-2-甲基-3-苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4r**): 产率 90%, 92%, 89% *ee*, 1.3∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV λ=296 nm; t^1_{minor}=52.768 min, t^1_{major}=18.300 min, t^2_{minor}=23.751 min, t^2_{major}=67.829 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33～7.28 (m, 2H), 7.24～7.21 (m, 1H), 7.15～7.13 (m, 2H), 6.78 (s, J=1.0 Hz, 2H), 6.27 (t, J=2.0 Hz, 1H), 5.88 (s, 1H), 4.72 (s, 1H), 3.79 (s, 6H), 3.25～3.20 (m, 1H), 2.43～2.34 (m, 2H), 2.06～2.01 (m, 1H), 0.86 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 161.3 (2C), 139.9, 137.5, 128.5 (2C), 127.6 (2C), 126.8, 102.2, 97.1 (2C), 85.7, 55.4 (2C), 38.1, 38.0, 29.7, 25.7, 6.8; HRMS (ESI) calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 370.1654, found 370.1667.

(1*R*,2*R*,3*R*,5*S*)-2-乙基-1-羟基-3,6-二苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4s**): 产率 56%, 99%, 98% *ee*, 1.3∶1 *dr*. HPLC: Daicel Chiralpak AD-H; hexane/*i*-PrOH (V∶V=80∶20); Flow: 1.0 mL/min; UV=296 nm; t^1_{minor}=35.614 min, t^1_{major}=24.911 min, t^2_{minor}=34.134 min, t^2_{major}=48.009 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54～7.53 (m, 2H), 7.34～7.28 (m, 4H), 7.23～7.20 (m, 1H), 7.18～7.12 (m, 3H), 5.90 (s, 1H), 4.83 (s, 1H), 3.28～3.24 (m, 1H), 2.41～2.36 (m, 1H), 2.16～2.13 (m, 1H), 2.02～1.98 (m, 1H), 1.83～1.76 (m, 1H), 1.30～1.20 (m, 1H), 0.58 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 139.9, 135.8, 129.4 (2C), 128.5 (2C), 127.7 (2C), 126.8, 125.3, 118.6 (2C), 102.9, 85.7, 45.2, 38.2, 26.4, 16.4, 14.7; HRMS (ESI) calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$ 324.3936, found 324.3938.

(1*R*,2*S*,3*R*,5*S*)-1-羟基-2-异丙基-3,6-二苯基-8-氧-6-氮杂双环[3.2.1]辛烷-7-酮(**4t**): 产率 59%, 98%, 99% *ee*, 9.5∶1 *dr*. HPLC: Daicel Chiralpak OD-H; hexane/*i*-PrOH (V∶V=90∶10); Flow: 1.0 mL/min; UV λ=268 nm; t^1_{minor}=31.051 min, t^1_{major}=28.705 min, t^2_{minor}=33.264 min, t^2_{major}=37.011 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56～7.54 (m, 2H), 7.39～7.36 (m, 2H), 7.33～7.30 (m, 2H), 7.25～7.18 (m, 4H), 5.75 (t, J=1.5 Hz 1H), 5.08 (s, 1H), 3.08～3.02 (m, 1H), 2.44～2.41 (m, 1H), 2.21～2.10 (m, 3H), 0.99 (d, J=7.0 Hz, 3H), 0.69 (d, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.7, 142.8, 136.0, 129.4 (2C), 128.9 (2C), 128.1 (2C), 126.9, 125.3, 118.8 (2C), 102.4, 85.6, 51.6, 39.2, 37.0, 26.6, 21.5, 20.0; HRMS (ESI) calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$ 338.1756, found 338.1752.

辅助材料(Supporting Information) 产物 **4a**～**4t** 的 ^{1}H NMR 和 ^{13}C NMR 谱图及 Chiral-HPLC 分析图. 这些材料可以免费从本刊网站(http://siocjournal.cn/)上下载.

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(Cheng, F.)

