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有机催化靛红亚胺与 1,2,4-三氮唑衍生物的不对称 *aza*-Mannich 反应

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摘要: 将 Takemoto 型 (硫) 脲衍生物用于催化靛红亚胺与 1,2,4-三氮唑的不对称 *aza*-Mannich 反应. 筛选出最佳催化剂体系为: 10%(摩尔分数) 的 1-[3,5-双 (三氟甲基) 苯基]-3-[(*1R,2R*)-2-(吡咯烷-1-基) 环己基] 硫脲催化剂 **1e**, 1 mL 乙醚为溶剂, 室温反应. 以 77%~90% 的产率和最高达 99% 的对映选择性获得手性 3-*N,N'*-缩酮-2-吲哚酮衍生物.

关键词: Takemoto 型 (硫) 脲衍生物; 不对称 *aza*-Mannich 反应; 靛红亚胺; 1,2,4-三氮唑
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含有 *N,N'*-缩酮-2-吲哚酮的骨架结构存在于很多天然产物和生物活性化合物中[1−13]. 然而, 由于 *N,N'*-缩酮结构不稳定, 其合成方法的研究远不如 *O,O'*-缩酮和 *O,N*-缩酮化合物广泛[14−19]. 尤其是非环手性 *N,N'*-缩酮化合物的制备更是有机合成领域中的难点. 靛红亚胺的不对称 *aza*-Mannich 反应是制备光学纯非环 *N,N'*-缩酮-2-吲哚酮的有效途径[20−22]. 1,2,4-三氮唑衍生物在医药领域的应用广泛, 具有抗菌[23]、镇痛消炎[24]、抗肿瘤[25] 等活性作用. 如伏立康唑、利巴韦林、来曲唑等. 因此, 以三氮唑为亲核试剂与靛红亚胺进行不对称 *aza*-Mannich 反应, 可以制备具有潜在生物活性的手性 *N,N'*-缩酮-2-吲哚酮衍生物. 2019 年, Zhang[21] 等报道了金鸡纳碱硫脲催化三氮唑与靛红亚胺的不对称 Mannich 反应, 以 90%~99% 的产率和 86%~97% 的立体选择性获得具有 C3 位 *N,N'*-缩酮结构的 3-氨基-2-吲哚酮衍生物. 目前, 三氮唑衍生物与靛红亚胺的反应仅有上述 1 篇文献报道, 催化剂为金鸡纳碱衍生物. 近年来, Takemoto 型催化剂被广泛应用于靛红亚胺的不对称 Mannich 反应[22,26−29], 我们将 Takemoto 型 (硫) 脲类衍生物催化剂 **1a−1l**, 应用于 *aza*-Mannich 反应 (图 1), 以期拓宽该反应的催化剂类型.

1　实验部分

1.1　试剂和仪器

催化剂 **1a−1l** 购买于上海大赛璐试剂有限公司; 硅胶 GF_{254} 薄层板及柱色谱分离用粒径 0.071~0.050 mm 硅胶购买于山西诺泰生物科技有限公司; 其他分析纯试剂通过市售渠道购买; ^{1}H NMR 和 ^{13}C NMR 光谱通过 Bruker Avance-500 型核磁共振谱仪 (德国 Bruker 公司) 测定; 以氘代 $CDCl_3$ 为溶剂, 以未氘代的 $CHCl_3$ 为内标 (分别为氢谱 7.26 和碳谱 77.0); 高分辨质谱 HRMS 的测定使用 Triple TOF 5600$^+$型质谱仪 (美国 Sciex 公司); 旋光值通过 A28579-T-CG APIII 型自动旋光仪 (美国 Rudolph 公司) 测定; 对映体过量值 (*ee*) 的测定使用 LC-20A 高效液相色谱仪 (日本岛津公司) 及 Daicel ChiralpakAS-H 手性色谱柱 (4.6 mm×250 mm,日本大赛璐公司).

1.2　不对称 *aza*-Mannich 反应的一般操作步骤

将靛红亚胺 **2**(0.1 mmol), 1,2,4-三氮唑 **3**(0.2 mmol) 和催化剂 **1**(10%(摩尔分数)), 乙醚 (Et_2O) 1 mL 加入 10 mL 干燥反应管中, 室温下搅拌反应 12~24 h, TLC 监测, 展开剂 (Hex∶EA = 1∶1), 反应结束后, 经快速柱层析分离纯化 (Hex∶EA = 2∶1),

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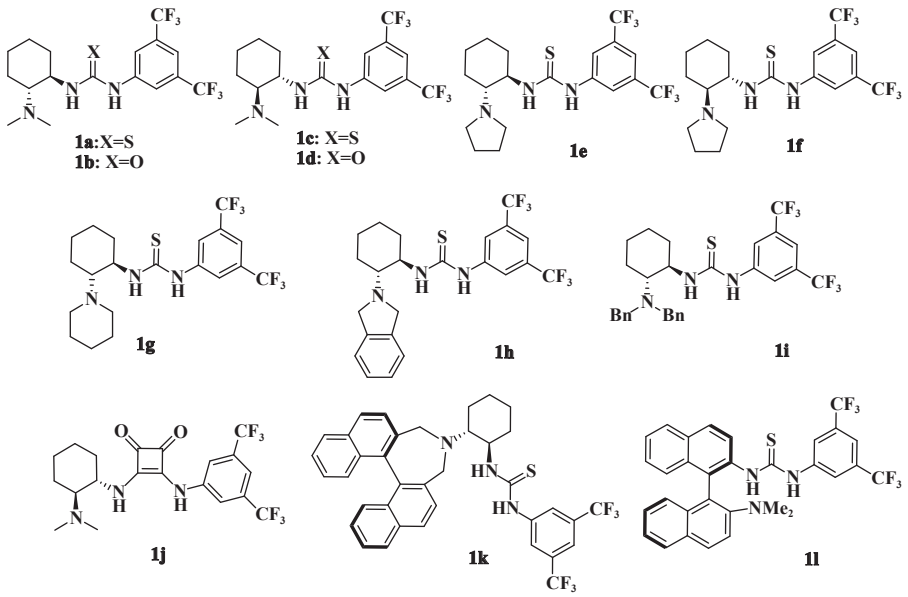


图 1　手性 Takemoto 型 (硫) 脲催化剂 **1a−1l** 的结构

Fig.1 The structure of chiral Takemoto′s (thio)urea catalysts **1a−1l**

得到目标产物 **4a−4l**. 其中化合物 **4c**、**4d**、**4f−4l** 为新化合物, 其 ^{1}H NMR、^{13}C NMR、HRMS、HPLC、熔点及比旋光值如下:

(*R*)-(1-苄基-5-氯-3-(1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4c: 白色固体; 81% yield; mp: 136.6~138.2 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.00 (s, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.37-7.26 (m, 6H), 6.71 (d, J = 8.5 Hz, 1H), 6.17 (s, 1H), 4.95 (q, J = 16.0 Hz, 2H), 1.43 (s, 9H). HR-ESI-MS *m/z*: 462.141 1 $[M+Na]^+$ (calcd for $C_{22}H_{22}ClN_5O_3Na$, 462.141 5); $[\alpha]_D^{25}$=−4.078 (c=0.56, $CHCl_3$) (67% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane：EtOH = 80：20, 1.0 mL/min, λ = 254 nm), t_R = 7.69 min (minor), 8.85 min (major).

(*R*)-(1-苄基-7-溴-3-(1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4d: 白色固体; 82% yield; mp: 68.9~71.2 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.00 (s, 1H), 7.85 (dd, J = 7.5, 1.0 Hz, 1H), 7.51 (dd, J = 8.0, 1.0 Hz, 1H), 7.31 (dd, J = 8.0, 6.5 Hz, 2H), 7.28-7.20 (m, 3H), 7.09-7.01 (m, 1H), 6.21 (s, 1H), 5.45 (q, J = 16.5 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 153.1, 152.8, 142.3, 140.3, 137.4, 136.2, 128.7, 128.4, 127.4, 126.2, 126.1, 125.1, 103.3, 82.2, 72.2, 45.4, 28.1. HR-ESI-MS *m/z*: 506.090 6 $[M+Na]^+$ (calcd for $C_{22}H_{22}BrN_5O_3Na$, 506.090 2); $[\alpha]_D^{25}$= −3.584 (c=0.53, $CHCl_3$) (48% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane：EtOH= 80：20, 1.0 mL/min, λ=254 nm), t_R = 8.82 min (minor), 10.92 min (major).

(*R*)-(1-苄基-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4e: 白色固体; 90% yield; mp: 193.3~195.8 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.84-7.79 (m, 1H), 7.35-7.25 (m, 7H), 7.14 (td, J = 7.5, 1.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.25 (s, 1H), 4.96 (dd, J =47.5, 16.0 Hz, 2H), 2.40 (s, 3H), 1.39 (s, 9H). HR-ESI-MS *m/z*: 442.195 7 $[M+Na]^+$ (calcd for $C_{23}H_{25}rN_5O_3Na$, 442.195 3); $[\alpha]_D^{25}$= −16.981 (c=0.50, $CHCl_3$) (99% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane：EtOH = 80：20, 1.0 mL/min, λ = 254 nm), t_R = 10.46 min (minor), 12.96 min (major).

(*R*)-(1-苄基-5-氟-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4f: 白色固体; 80% yield; mp: 179.2~182.7 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.71 (s, 1H), 7.43-7.35 (m, 3H), 7.32 (dd, J = 10.0, 4.5 Hz, 2H), 7.28-7.24 (m, 1H), 7.18 (td, J = 9.0, 2.5 Hz, 1H), 6.92 (dd, J = 8.5, 4.0 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 2.19 (s, 3H), 1.30 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 161.2, 160.4, 158.4, 154.5, 144.8, 139.8, 136.3, 129.6, 129.5 (d, J = 22.4 Hz), 128.4,

128.1, 117.9, 117.7, 113.6, 113.4, 111.8 (d, J = 7.7 Hz), 81.3, 74.3, 44.1, 28.7, 14.6. HR-ESI-MS *m/z*: 460.176 1 $[M+Na]^+$ (calcd for $C_{23}H_{24}FN_5O_3Na$, 460.176 8); $[\alpha]_D^{25}$=−4.09 (c=0.12, $CHCl_3$) (76% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane∶EtOH = 80∶20, 1.0 mL/min, λ = 254 nm),t_R = 8.03 min (minor), 9.30 min (major).

(*R*)-(1-苄基-5-氯-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4g: 白色固体; 81% yield; mp: 172.1~174.4 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.35-7.26 (m, 6H), 6.68 (d, J = 8.5 Hz, 1H), 6.20 (d, J = 6.0 Hz, 1H), 5.00 (d, J = 16.0 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 2.40 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 162.4, 153.2, 142.3, 141.2, 134.1, 131.2, 129.3, 129.0, 128.1, 127.3, 127.1, 126.9, 111.2, 82.0, 72.5, 44.6, 28.1, 14.1; HR-ESI-MS *m/z*: 476.146 5 $[M+Na]^+$ (calcd for $C_{23}H_{24}ClN_5O_3Na$, 476.146 0); $[\alpha]_D^{25}$=−1.44 (c=0.62, $CHCl_3$) (73% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane∶EtOH= 80∶20, 1.0 mL/min, λ = 254 nm), t_R = 7.77 min (minor), 8.90 min (major).

(*R*)-(1-苄基-5-溴-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4h: 白色固体; 86% yield; mp: 168.1~172.2 ℃; ^{1}H NMR (500 MHz, DMSO) δ 9.00 (s, 1H), 8.73 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.51 (dd, J = 8.5, 2.0 Hz, 1H), 7.38 (d, J = 7.0 Hz, 2H), 7.33-7.29 (m, 2H), 7.26 (dd, J = 8.5, 6.0 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 2.19 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, DMSO) δ 170.5, 161.2, 154.4, 144.7, 142.8, 136.1, 134.1, 130.1, 129.3, 128.3, 128.2, 128.0, 115.5, 112.7, 81.3, 74.0, 44.1, 28.6, 14.5. HR-ESI-MS *m/z*: 520.095 5 $[M+Na]^+$ (calcd for $C_{23}H_{24}BrN_5O_3Na$, 520.096 1); $[\alpha]_D^{25}$=−8.36 (c=0.58, $CHCl_3$) (77% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane∶EtOH = 80∶20, 1.0 mL/min, λ = 254 nm), t_R = 8.14 min (minor), 9.36 min (major).

(*R*)-(1-苄基-5-甲基-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4i: 白色固体; 85% yield; mp: 174.0~176.7 ℃; ^{1}H NMR (500 MHz, DMSO) δ 8.89 (s, 1H), 8.64 (s, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.30 (dd, J = 10.0, 5.0 Hz, 3H), 7.25 (t, J = 7.0 Hz, 1H), 7.10 (dd, J = 8.0, 1.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.96 (d, J = 16.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 2.24 (s, 3H), 2.18 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO) δ 170.9, 161.0, 144.6, 141.2, 136.6, 133.0, 131.6, 129.3, 128.3, 128.1, 126.0, 110.5, 81.0, 74.6, 44.0, 28.8, 21.6, 14.6. HR-ESI-MS *m/z*: 456.201 2 $[M+Na]^+$ (calcd for $C_{24}H_{27}N_5O_3Na$, 456.201 9); $[\alpha]_D^{25}$=−10.37 (c=0.56, $CHCl_3$) (90% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane∶EtOH= 80∶20, 1.0 mL/min, λ= 254 nm), t_R = 10.62 min (minor), 12.72 min (major).

(*R*)-(1-苄基-5-甲氧基-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4j: 白色固体; 85% yield; mp: 159.4~162.5 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.37-7.26 (m, 5H), 6.83 (dd, J = 8.5, 2.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 6.23 (s, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.89 (d, J = 16.0 Hz, 1H), 3.76 (s, 3H), 2.40 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 156.6, 153.3, 142.4, 135.9, 134.6, 128.9, 127.9, 127.1, 116.2, 113.7, 110.8, 81.7, 72.9, 55.8, 44.5, 28.1, 14.2; HR-ESI-MS *m/z*: 472.196 1 $[M+Na]^+$ (calcd for $C_{24}H_{27}N_5O_3Na$, 472.196 7); $[\alpha]_D^{25}$=−1.44 (c=0.62, $CHCl_3$) (76% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane∶EtOH = 80∶20, 1.0 mL/min, λ = 254 nm), t_R = 13.04 min (minor), 21.52 min (major).

(*R*)-(1-苄基-7-氟-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4k: 白色固体; 83% yield; mp: 182.0~184.2 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.59 (dd, J = 5.5, 3.0 Hz, 1H), 7.39-7.27 (m, 5H), 7.12-7.06 (m, 2H), 6.24 (s, 1H), 5.09 (q, J = 15.5 Hz, 2H), 2.39 (s, 3H), 1.39 (s, 9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 162.4, 153.1, 148.6, 146.6, 142.3, 135.9, 128.7, 128.2, 128.0 (d, J = 32.7 Hz), 127.4, 124.5 (d, J = 6.2 Hz), 122.6, 119.5 (d, J = 19.4 Hz), 81.9, 72.6, 46.2, 28.1, 14.1. HR-ESI-MS *m/z*: 460.176 1 $[M+Na]^+$ (calcd for $C_{23}H_{24}FN_5O_3Na$, 460.176 6); $[\alpha]_D^{25}$=−11.13 (c=0.43, $CHCl_3$) (77% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane∶EtOH= 80∶20, 1.0 mL/min, λ = 254 nm), t_R = 8.32 min (minor), 10.39 min (major).

(*R*)-(1-苄基-7-溴-3-(3-甲基-1H-1,2,4-三唑-1-)-2-吲哚酮-3-) 氨基甲酸叔丁酯 4l: 白色固体; 82% yield; mp: 168.9~171.4 ℃; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.92 (s, 1H), 7.76 (dd, J = 7.5,1.0 Hz, 1H), 7.49 (dd, J = 8.0, 1.0 Hz, 1H), 7.34-7.23 (m, 5H), 7.03 (t, J = 8.0 Hz, 1H), 6.23 (s, 1H), 5.45 (q, J = 16.5 Hz, 2H), 2.39 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 162.5, 153.1, 142.3, 140.4, 137.3, 136.4, 128.7, 127.3, 126.2, 125.7, 125.0, 103.3, 82.0, 72.0, 45.3, 28.1, 14.1. HR-ESI-MS *m/z*: 520.095 5 $[M+Na]^+$ (calcd for $C_{23}H_{24}BrN_5O_3Na$, 520.095 0); $[\alpha]_D^{25}$=−0.127 (c=0.37, $CHCl_3$) (79% *ee*); HPLC (Daicel Chiralcel ID, *n*-hexane：EtOH = 80：20, 1.0 mL/min, λ = 254 nm), t_R = 8.56 min (minor), 11.60 min (major).

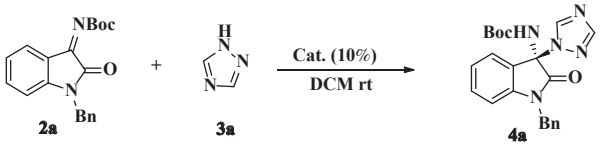
2 结果与讨论

2.1 Takemoto 型 (硫) 脲 1a−1l 的 *aza*-Mannich 反应

将催化剂 **1a−1l** 应用于靛红亚胺 **2a** 与 1,2,4-三氮唑 **3a** 的不对称 *aza*-Mannich 反应, 考察催化剂的催化性能. 根据文献报道的最优条件[21], 选用二氯甲烷为溶剂, 10%(摩尔分数) 催化剂用量, 室温反应 12 h. 反应结果见表 1.

表 1　靛红亚胺与 1,2,4-三氮唑的不对称 *aza*-Mannich 反应的结果[a]

Table 1　Asymmetric *aza*-Mannich reaction of isatin imine with 1,2,4-triazole[a]



Entry	Catalyst	Yield/%[b]	*ee*/%[c]	Conf.[d]
1	**1a**	81	4	*R*
2	**1b**	83	4	*R*
3	**1c**	80	10	*S*
4	**1d**	85	26	*S*
5	**1e**	**87**	**61**	***R***
6	**1f**	81	0	–
7	**1g**	75	14	*R*
8	**1h**	86	48	*R*
9	**1i**	84	20	*S*
10	**1j**	76	0	–
11	**1k**	76	5	*R*
12	**1l**	78	6	*R*

a. Reaction condition: Isatin-derived ketimine(0.10 mmol), 1,2,4-triazole (0.20 mmol) and catalysts(0.01mmol) in DCM (1 mL), the mixture was reacted at rt for 12 h; b. isolated yield; c. Determined by HPLC analysis (Chiralpak ID-H); d. The configuration was determined by comparison with the optical rotation data of the literature[21].

由表 1 结果可以看出 12 种催化剂 **1a−1l** 在二氯甲烷中均能顺利催化靛红亚胺和 1,2,4-三氮唑的不对称 *aza*-Mannich 反应, 以 75%~87% 的产率获得目标产物. 其中 (*R*,*R*)-*N*-吡咯硫脲催化剂 **1e** 表现出最好的的催化性能, 得到 61% *ee*(Entry 5). 通过测定其旋光值, 并与文献的数据进行比较[21], 确定主要产物的绝对构型为 *R*. 奇怪的是, 当以 (*S*,*S*)-*N*-吡咯硫脲催化剂 **1f** 催化该反应, 得到了消旋的产物. 此外, 当硫脲催化剂环己胺 N 上的取代的基团更大时, 不利于催化剂的诱导作用, 所得相应目标产品的立体选择性均有所下降 (Entry 7−9 vs Entry 5). 综上, 筛选出最优催化剂为 **1e**.

2.2 反应条件的优化

将催化剂 **1e** 应用于靛红亚胺 **2a** 和 1,2,4-三氮唑 **3a** 的不对称 *aza*-Mannich 反应中. 通过考察不同种类溶剂、温度、催化剂负载量等条件对催化效能的影响, 以期优化反应条件, 提高反应的立体选择性. 结果见表 2.

表 2 1e 催化靛红亚胺与苯胺的不对称 *aza*-Mannich 反应的条件筛选[a]

Table 2 Screening of reaction condition for the asymmetric *aza*-Mannich reaction catalyzed by **1e**[a]

Entry	Solvent	Temp./℃	Cat. Loading /%(Mole fraction)	Yield/%[b]	*ee*/%[c]
1	DCM	rt	10	87	61
2	Et_2O	rt	10	88	86
3	$CHCl_3$	rt	10	85	64
4	THF	rt	10	78	55
5	PhMe	rt	10	80	76
6	CH_3CN	rt	10	75	7
7	MTBE	rt	10	88	26
8	Xylene	rt	10	78	9
9	Et_2O	0	10	85	74
10	Et_2O	−10	10	70	69
11	Et_2O	rt	20	89	85
12	Et_2O	rt	5	85	78
13[d]	Et_2O	rt	10	83	76
14[e]	Et_2O	rt	10	89	70

a. Reaction condition: Isatin derived imine **2a** (0. 10 mmol), 1,2,4-triazole **3a** (0.20 mmol) and **1e**(0.01mmol) in solvent (1 mL) the mixture was reacted for 12~24 h; b. isolated yield; c. Determined by HPLC analysis (Chiralpak ID-H); d. 2 mL of solvent; e. 0.4 nm MS(about 200 mg).

由表 2 可得出以下结果: (1) 溶剂对反应的产率和立体选择性有影响: 以乙醚为溶剂时获得了最好的对映选择性 (86% *ee*, Entry 2) 而在乙腈和二甲苯的条件下, 立体选择性分别下降至 7% *ee* 和 9% *ee* (Entry 6, 8); (2) 温度对反应立体选择性有一定的影响: 当温度降至 0 ℃ 时, 反应的产率和 *ee* 值均有所下降 (Entry 9 vs Entry 2). 当温度继续降至−10 ℃ 时, 反应速度变得更慢, 产品的立体选择性下降至 69% *ee* (Entry 10); (3) 将催化剂用量增加至 20%(摩尔分数), 产品的 *ee* 值和产率没有得到提高 (Entry 11 vs Entry 2), 而将用量降至 5%(摩尔分数), 反应的产率和立体选择性均有所下降 (Entry 12 vs Entry 2); (4) 当稀释反应浓度一倍, 即溶剂用量增至 2 mL 时, 反应的产率和立体选择性均有所下降 (Entry 13 vs Entry 2); (5) 加入 0.4 nm 分子筛, 产品的 *ee* 值明显下降至 70%(Entry 14 vs Entry 2). 基于以上结果, 筛选出的最佳反应体系为: 10%(摩尔分数) 催化剂 **1e**, 1 mL Et_2O, 室温反应.

2.3 普适性的考察

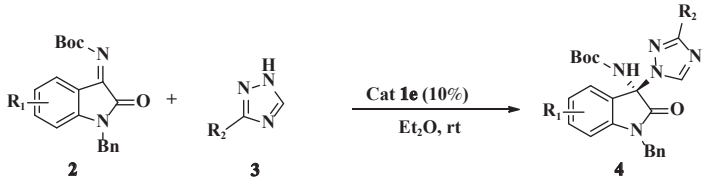
将上述筛选的最佳催化剂体系用于 8 种不同取代靛红亚胺和 2 种 1,2,4-三氮唑应的不对称 *aza*-Mannich 反应中, 扩展该反应底物的范围, 考察催化剂体系对反应的普适性, 结果见表 3.

由表 3 可以看出: 在最优反应条件下, 多种取代靛红亚胺和 1,2,4-三氮唑及 3-甲基三氮唑的不对称 *aza*-Mannich 反应均能够顺利进行, 以 77%~90% 的产率获得相应的目标产物 **4a−4m**. 其中苯环上没有取代基的苄基靛红亚胺 **2a** 为底物与不同三氮唑的反应得到了最佳的立体选择性, 分别为 86% *ee* 和 99% *ee*(Entry 1, Entry 5). 与 1,2,4-三氮唑相比, 以 3-甲基-1,2,4-三氮唑为底物, 明显能够提高反应的立体选择性 (Entry 5−7,12 vs Entry1−4). 综上, 靛红亚胺上取代基的种类和位置以及三氮唑结构上的甲基对反应的立体选择性均有影响, 机理尚不清楚, 有待于进一步研究.

根据得到产品的绝对构型, 提出可能的过渡态如图 2 所示: 双功能催化剂 **1e** 的硫脲结构通过双氢键定位和活化靛红亚胺, 同时, 催化剂的叔胺氮与三氮唑形成氢键, 进而去质子活化的三氮唑从 *re*-面进攻亚胺基, 得到 *R* 构型产品.

表 3 不同取代靛红亚胺与三氮唑的不对称 *aza*-Mannich 反应[a]

Table 3 Generility of the enantioselective *aza*-Mannich reaction of isatin derived imines with 1,2,4-triazole[a]



Entry	Product	R_1	R_2	Yield/%[b]	*ee*/%[c]
1	**4a**	H	H	88	86
2	**4b**	5-F	H	83	50
3	**4c**	5-Cl	H	80	67
4	**4d**	7-Br	H	79	57
5	**4e**	H	Me	90	99
6	**4f**	5-F	Me	80	76
7	**4g**	5-Cl	Me	81	73
8	**4h**	5-Br	Me	80	60
9	**4i**	5-Me	Me	85	90
10	**4j**	5-OMe	Me	77	60
11	**4k**	7-F	Me	80	77
12	**4l**	7-Br	Me	78	79

a. Reaction condition: Isatin derived imines (0.10 mmol), 1,2,4-triazole (0.20 mmol) and **1e** (0.01 mmol) in Et_2O (1 mL), the mixture was reacted at rt for 12~24 h; b. isolated yield; c. Determined by HPLC analysis (Chiralpak ID-H).

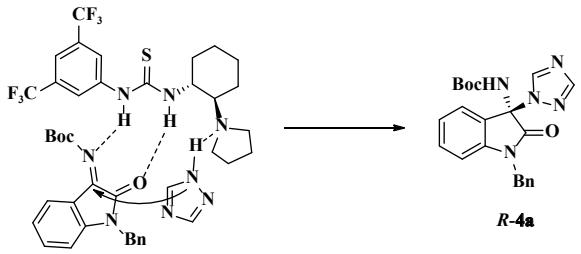


图 2 可能的过渡态模型

Fig.2 Proposed transition state model

3 结论

我们将 12 种 Takemoto 型 (硫) 脲催化剂应用于苄基靛红亚胺与 1,2,4-三氮唑的不对称 *aza*-Mannich 反应中. 通过考察催化剂结构、用量、溶剂的种类、反应液浓度、温度及分子筛等条件对该反应的立体选择性的影响, 筛选出最优催化剂条件, 并应用于不同取代靛红亚胺的和不同取代苯胺不对称 *aza*-Mannich 反应, 以最高达 99% 的对映选择性获得手性 3-*N*,*N*′-缩酮-2-吲哚酮衍生物. 扩展了该反应中催化剂的类型. 但是, 反应普适性还有待于提高.

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Organocatalyzed Enantioselective *Aza*-Mannich Reaction of Isatin-derived Ketimines and 1,2,4-Triazoles

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Abstract: Takemoto′s (thio)urea derivatives were applied in the asymmetric *aza*-Mannich reaction of isatin derived ketimines and 1,2,4-triazoles. The screened optimal conditions were determined to be 10%(Mole fraction) loading catalyst (*R,R*)-*N*-pyrrole thiourea **1e** in Et_2O (1 mL) at rt. The different substituted substrates were evaluated for the generality of this reaction, the desired chiral 3,3-diamino-2-oxindoles bearing *N,N*’-ketal structural motif were obtained in 77%~90% yields with up to 99% enantiomeric excess (*ee*).

Key words: Takemoto′s (thio)urea derivatives; asymmetric *aza*-Mannich reaction; isatin derived ketimines; 1,2,4-triazoles