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金鸡纳生物碱衍生物催化 β-萘酚和 N-Ts 芳香酰亚胺的不对称 *aza-Friedel-Crafts* 反应

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摘要：将金鸡纳生物碱衍生物用于催化 β-萘酚和芳香酰亚胺的不对称 *aza-Friedel-Crafts* 反应制备 Betti 碱衍生物. 考察溶剂、温度及催化剂用量对反应催化性能的影响. 结果表明，最佳催化条件为 10% 催化剂 **1c**，甲苯为溶剂，0 ℃反应. 得到了 70% ~86% 的化学产率和最高达 80% ee 的对映选择性.

关键词：金鸡纳生物碱衍生物；不对称催化；*aza-Friede-Crafts* 反应；β-萘酚；Betti 碱
中图分类号：O621.3；O643.3　　**文献标志码：**A

芳香族化合物与醛、酮、活化烯烃及亚胺的 Friedel-Crafts 反应是形成 C—C 键的重要方法[1-3]. 不对称 *aza-Friedel-Crafts* 反应更是有机合成领域中的重要反应，其亲核试剂不需要活化，得到的芳胺产物是许多生物活性的天然产物及合成药物的骨架结构[4-5]. 此外，基于 β-萘酚的不对称 *aza-Friedel-Crafts* 是获得手性 Betti 碱的最有效方法. Betti 碱是一类高效的手性配体，广泛应用于多种金属催化的不对称反应中[6-8]. 目前，有机催化 β-萘酚的不对称 *aza-Friedel-Crafts* 研究还很少[9-11]. 2010 年，Niu 等[12]首次报道了锌催化 β-萘酚和 *N*-Ts(*N*-对甲基苯磺酰基)芳香酰亚胺的不对称 *aza-Friedel-Crafts* 反应，得到了 74% ~98% ee 的对映选择性. 2011 年，Liu 等[13]报道了有机催化的 α-萘酚为底物的反应，仅尝试了对氯苯甲酰亚胺和 β-萘酚 *aza-Friedel-Crafts* 反应，得到了 62% ee 的结果. 我们将多种金鸡纳生物碱衍生物 **1a-g**(Fig. 1)作为有机催化剂用于 β-萘酚和 *N*-Ts 芳香酰亚胺的不对称 *aza-Friedel-Crafts*.

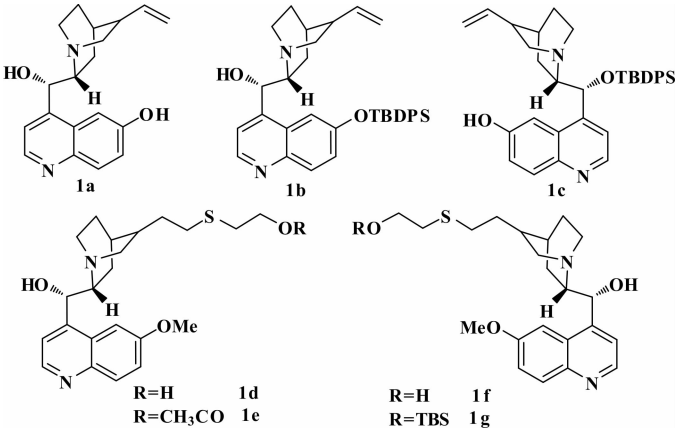

图 1 催化剂 **1a-g** 的结构
Fig. 1 The structure of catalysts **1a-g**

1 实验部分

1.1 试剂和仪器

Bruker Avance-500 型核磁共振谱仪(均以 $CDCl_3$ 为溶剂，TMS 为基准物质，德国 Bruker 公司)；MICROMASS Quattro Premier 型质谱仪(美国 waters 公司)；LC-20A 高效液相色谱仪(日本岛津公司)，Daicel Chiralpak AD-H，OD-H 手性色谱柱

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(日本大赛璐公司). 奎宁为 Acros 试剂; 奎尼丁为 Fluka 试剂, 其他试剂均为市售分析纯产品. 芳香醛亚胺根据文献方法合成[14-15]. 催化剂 **1a-g** 根据文献方法合成[16].

1.2 不对称 *aza-Friedel-Crafts* 反应

将 β-萘酚(0.5 mmol), 芳香酰亚胺(0.1 mmol)和催化剂(0.01 mmol)溶于 1 mL 甲苯, 0 ℃冰水浴中反应 24 h, TLC 监测反应. 反应结束后, 经硅胶柱层析分离, 正己烷∶乙酸乙酯(12∶1)洗脱, 得到产品 **3a-j**.

3a ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.41-7.37 (m, 1H), 7.36-7.22 (m, 4H), 7.21 (d, J = 7.5 Hz, 2H), 6.85 (d, J =9.0 Hz, 1H), 6.62 (d, J =8.0 Hz, 2H), 6.39(s, 1H), 2.08(s, 3H); HPLC(Daicel Chiralpak AD-H, V_{hex}∶V_{iPrOH}=90∶10, 1.0 mL/min, 235 nm), t_R:26.9 min (minor), 35.1 min (major).

3b ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48-7.42 (m, 5H), 7.30-7.25 (m, 3H), 7.19-7.14 (m, 1H), 6.97-6.92 (m, 2H), 6.85 (d, J = 9.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 2.15 (s, 3H); HPLC(Daicel Chiralpak AD-H, V_{hex}∶V_{iPrOH}=90∶10, 1.0 mL/min, 235 nm), t_R: 21.7 min (major), 25.9 min (minor).

3c ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.67 (m, 2H), 7.58 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.41-7.27 (m, 4H), 7.22-7.19(m, 1H), 7.15-7.05(m, 1H), 6.94 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.70 (s, 1H), 5.91 (s, 1H), 2.27 (s, 3H); HPLC (Daicel Chiralpak AD-H, V_{hex}∶V_{iPrOH}=90∶10, 1.0 mL/min, 235 nm), t_R: 19.1 min (major), 28.6 min (minor).

3d ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1H), 7.75(s, 1H), 7.70(d, J = 8.5 Hz, 2H), 7.57(d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.32-7.28 (m, 2H), 7.10-7.07 (m, 2H), 6.91(d, J=8.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 1H), 6.69 (d, J = 6.0 Hz, 1H), 6.03 (d, J = 6.0 Hz, 1H), 2.27 (s, 3H); HPLC (Daicel Chiralpak AD-H, V_{hex}∶V_{iPrOH}=90∶10, 1.0 mL/min, 235 nm), t_R: 21.5 min (major), 36.1 min (minor).

3e ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 1H), 7.72-7.70 (m, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.63-7.58 (m, 3H), 7.51-7.45 (m, 3H), 7.39-7.36 (m, 1H), 7.25-7.20 (m, 2H), 7.10(d, J =8.0 Hz, 2H), 6.67(d, J =8.5 Hz, 1H), 6.37(d, J= 6.5 Hz, 1H), 5.95 (d, J =6.5 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8, 143.9, 138.8, 137.1, 134.1, 132.0, 130.5, 129.2, 128.9, 128.4, 127.3, 126.8, 126.3, 125.5, 125.2, 124.8, 123.1, 122.0, 120.0, 118.1, 54.0, 21.3; HPLC (Daicel Chiralpak AD-H, V_{hex}∶V_{iPrOH}=90∶10, 1.0 mL/min, 235 nm), t_R: 16.0 min (major), 29.7 min (minor).

3f ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.46-7.29 (m, 4H), 7.18-7.16 (m, 3H), 6.80 (d, J = 9.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 2H), 6.56 (s, 1H), 6.38 (s, 1H), 5.95 (s, 1H), 2.10 (s, 3H); HPLC (Daicel Chiralpak OD-H, V_{hex}∶V_{iPrOH}=98∶2, 0.6 mL/min,235 nm), t_R: 252.5 min (major), 268.5 min (minor).

3g ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.48 (d, J =9.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.30-7.22 (m, 4H), 7.20(dd, J = 0.5, 8.0 Hz, 1H), 7.03(t, J=8.0 Hz, 1H), 6.86 (d, J =8.5 Hz, 1H), 6.57 (d, J =8.0 Hz, 2H), 6.30 (d, J =10.0 Hz, 1H), 2.04(s, 3H); HPLC (Daicel Chiralpak OD-H, V_{hex}∶V_{iPrOH}=95∶5, 0.6 mL/min 235 nm), t_R: 38.5 min (major), 44.1 min (minor).

3h ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5, 1H), 7.65 (d, J = 8.0, 1H), 7.50 (d, J = 9.0, 1H), 7.42-7.38 (m, 1H), 7.33-7.25 (m, 5H), 7.12-7.08 (m, 1H), 7.06-7.01 (m, 2H), 6.84 (d, J = 8.5, 1H), 6.66-6.40 (m, 3H), 6.37(d, J = 9.5, 1H), 2.24 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 142.7, 139.9, 138.1, 136.2, 132.3, 129.7, 129.5, 129.0,

128.6, 128.2, 127.4, 127.1, 126.6, 126.4, 123.7, 123.3, 121.9, 118.2, 117.7, 54.4, 21.4, 21.2; HPLC (Daicel Chiralpak OD-H, V_{hex} : $V_{i\,PrOH}$ = 95 : 5, 0.3 mL/min, 235 nm), t_R: 71.4 min(major), 89.4 min(minor).

3i ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.45-7.39 (m,1H),7.35-7.26 (m, 4H), 6.95-6.88 (m, 3H), 6.84 (J= 8.0 Hz, 3H), 6.67 (d, J=8.0 Hz, 1H), 6.39-6.32 (m, 1H), 2.10 (s, 3 H); HPLC (Daicel Chiralpak OD-H, V_{hex} : $V_{i\,PrOH}$ = 90 : 10, 0.6 mL/min, 235 nm), t_R: 17.7 min (minor), 20.0 min (major).

3j ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 2H), 7.54 (d, J = 9.0 Hz, 1H), 7.43-7.39 (m, 1H), 7.33-7.26 (m, 3H), 7.23 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 6.84 (d, J =9.0 Hz, 1H), 6.64 (d, J =8.0 Hz, 2H), 6.34 (d, J =10.0 Hz, 2H), 2.09 (s, 3H); HPLC (Daicel Chiralpak AD-H, V_{hex} : $V_{i\,PrOH}$ = 95 : 5, 0.8 mL/min, 235 nm), t_R: 26.0 min (minor), 31.8 min (major).

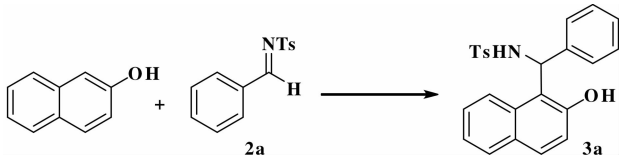
2 结果与讨论

2.1 催化剂1a-g催化不对称*aza-Friede-Crafts*反应

将催化剂**1a-g**用于β-萘酚和苯甲酰亚胺的不对称*aza-Friedel-Crafts*反应，考察各种催化剂的催化性能.并考察温度、溶剂及催化剂用量对反应立体选择性的影响.结果见表1.

表1 β-萘酚和苯甲酰亚胺的不对称*aza-Friedel-Crafts*反应条件[a]

Table 1 Screening of Reaction Conditions for the Asymmetric *aza-Friedel-Crafts* reaction[a]



Entry	Cat	Solvent	T/℃	Cat loading/(mmol%)	Yield/%[b]	ee/%[c]	Config.
1	**1a**	PhMe	0	20	72	26	*S*
2	**1b**	PhMe	0	20	86	−53	*R*
3	**1c**	PhMe	0	20	87	63	*S*
4	**1d**	PhMe	0	20	76	−30	*R*
5	**1e**	PhMe	0	20	71	−8	*R*
6	**1f**	PhMe	0	20	80	33	*S*
7	**1g**	PhMe	0	20	78	33	*S*
8	**1c**	$CHCl_3$	0	10	83	55	*S*
9	**1c**	CH_2Cl_2	0	10	81	60	*S*
10	**1c**	CH_3CN	0	10	87	51	*S*
11	**1c**	acetone	0	10	63	44	*S*
12	**1c**	*n*-Hexane	rt	10%	–	–	–
13	**1c**	*c*-Hexane	rt	10	–	–	–
14	**1c**	PhMe	rt	10	87	45	*S*
15	**1c**	PhMe	0	10	85	64	*S*
16	**1c**	PhMe	−20	10	72	62	*S*
17	**1c**	PhMe	0	5	83	59	*S*

a. All of the reactions were performed with N-Tosyl benzaldimine (0.10 mmol) and β-naphthol (0.50 mmol) in different solvent for 5 ~ 6 h; b. Isolated yield; c. Determined by HPLC analysis (Chiralpak AD-H).

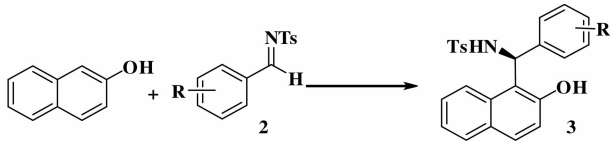
由表 1 结果可以得出以下结论：(1)7 种催化剂在甲苯中均能顺利催化 β-萘酚和苯甲酰亚胺的不对称 *aza-Friedel-Crafts* 反应，得到 71% ~87% 的产率. 其中由奎宁衍生的催化剂 **1c** 得到了最好的对映选择性(63% ee，entry 3)，其构型经过测定旋光值，并与文献对照[12]，确定为 *S* 构型. 而由奎尼丁衍生的催化剂 **1b** 催化该反应得到了 *R* 构型的产物(−53% ee，entry 2)；(2)溶剂对反应的立体选择性有明显的影响，其中甲苯为最适合溶剂；(3)反应温度对立体选择性有一定的影响，室温时得到了 45% ee，当温度降至 0 ℃，产物的对映体过量值增加了 19% ee (entry 15 vs entry 14). 但是，将温度降至−20 ℃，产物的 ee 值没有提高，而产率有所下降(entry 16)；(4)催化剂用量对反应的立体选择性有影响，10% 和 20% 的用量得到相似的结果(entry 15 vs entry 3)，将用量减至 5%，产物的 ee 值有所下降(59% ee，entry 17). 综上所述，筛选出最佳催化剂体系为：催化剂 **1c**，10% 的用量，以甲苯为溶剂，0 ℃反应.

2.2 底物的扩展

将筛选出的催化条件应用于不同取代苯甲酰亚胺的不对称 *aza-Friedel-Crafts* 反应中，考察催化剂体系的普适性. 结果见表 2.

表 2 β-萘酚和芳香酰亚胺的不对称 *aza-Friedel-Crafts* 反应[a]

Table 2 Asymmetric *aza-Friedel-Crafts* Reaction of 2-Naphthol with Tosyl imines[a]



Entry	Product	*R*	Yield/%[b]	ee/%[c]
1	**3a**	H	86	64
2	**3b**	2-F	80	73
3	**3c**	2-Cl	83	78
4	**3d**	2-Br	81	80
5	**3e**	2-CF_3	78	70
6	**3f**	3-Cl	74	57
7	**3g**	3-Br	82	64
8	**3h**	3-CH3	80	62
9	**3i**	4-Cl	75	57
10	**3j**	4-F	70	50

a. All of the reactions were performed with N-Tosyl benzaldimine (0.10 mmol), β-naphthol (0.50 mmol) and catalyst (0.01 mmol) in 1 mL toluene at 0 ℃; b. Isolated yield; c. Determined by HPLC analysis (Chiralpak AD-H, OD-H).

由表 2 可以看出，催化剂 **1c** 能够顺利地催化不同取代的苯甲酰亚胺和 β-萘酚的不对称 *aza-Friedel-Crafts* 反应，得到 70% ~86% 的产率. 邻位取代的苯甲酰亚胺为底物的反应得到了好的对映选择性，其中邻溴苯甲酰亚胺和 β-萘酚的反应得到了最高的 ee 值(80% ee，entry 4). 对位取代的底物在该反应中表现出差的立体选择性，对氟苯甲酰亚胺的反应得到了最低的 ee 值(50% ee，entry 10)，说明芳环上取代基种类和的位置对反应的立体选择性有一定的影响.

3 结　论

我们将金鸡纳生物碱衍生物用于有机催化的芳香醛亚胺和 β-萘酚的不对称 *aza-Friedel-Crafts* 反应. 筛选出最佳的催化剂体系为：10% 的奎宁衍生物催化剂 **1c**，在甲苯中 0 ℃反应. 将筛选出来的催化剂体系应用于不同取代的苯甲酰亚胺的反应，以邻溴苯甲酰亚胺为底物的反应获得了最好的立体选择性(80% ee). 催化剂体系对底物普适性的提高还有待于进一步研究.

参考文献:

[1] Szatmari I, Martinek T A, Lazar L, *et al*. Synthesis of 2, 4-Diaryl-3,4-dihydro-2*H*-naphth [2,1-*e*] [1,3] oxazines and study of the effects of the substituents on their ring-chain tautomerism[J]. *Eur J Org Chem*, 2004, **10**: 2231-2238.

[2] Bandini M, Melloni A, Umani-Ronchi A. New catalytic approaches in the stereoselective friedel-crafts alkylation reaction[J]. *Angew Chem Int* Ed, 2004, **43**:550-556.

[3] Bandini M, Melloni A, Tommasi S, *et al*. A journey across recent advances in catalytic and stereoselective alkylation of indoles[J]. *Synlett*, 2005, **8**:1199-1222.

[4] Poulsen T B, Jørgensen K A. Catalytic asymmetric friedel-crafts alkylation reactions copper showed the way [J]. *Chem Rev*, 2008, **108**:2903-2915.

[5] Shirakawa S, Berger R, Leighton J L. Enantioselective friedel-crafts alkylations with benzoylhydrazones promoted by a simple strained silacycle reagent[J]. *J Am Chem Soc*, 2005, **127**:2858-2859.

[6] Kocovsky P, Vyskocil S, Smrcina M. Non-symmetrically substituted 1,1'-binaphthyls in enantioselective catalysis [J]. *Chem Rev*, 2003, **103**:3213-3246.

[7] Cimarelli C, Palmieri G, Volpini E. A practical stereoselective synthesis of secondary and tertiary aminonaphthols: chiral ligands for enantioselective catalysts in the addition of diethylzinc to benzaldehyde[J]. *Tetrahedron: Asymmetry*, 2002, **13** :2417-2426.

[8] Ji J-X, Wu J, Au-Yeung T T-L, *et al*. Highly enantioselective phenyl transfer to aryl adehydes catalyzed by easily accessible chiral tertiary aminonaphthol [J]. *J Org Chem*, 2005, **70**: 1093-1096.

[9] a. Brandes S, Bella M, Kjoersgaard A, *et al*. Chirally aminated 2-naphthols-organocatalytic synthesis of non-biaryl atropisomers by asymmetric friedel-crafts amination [J]. *Angew Chem Int Ed*, 2006, **45** :1147-1151.
b. Nan P, Chen J, Sun X. Study on the asymmetric aminohydrexy lation of olefins catalyzed by afree recoverable and reusable ligand[J]. *J Mol Catal* (China) (分子催化), 2011, **25**(2):109-113.

[10] Liu T-Y, Cui H-L, Chai Q, *et al*. Organocatalytic asymmetric friedel-crafts alkylation/ cascade reactions of naphthols and nitroolefins[J]. *Chem Commun*, 2007, **7**: 2228-2230.

[11] Hong L, Wang L, Sun W, *et al*. Organocatalytic asymmetric friedel-crafts alkylation/cyclization cascade reaction of 1-naphthols and α,β-unsaturated aldehydes: an enantioselective synthesis of chromanes and dihydrobenzopyranes[J]. *J Org Chem*, 2009, **74**:6881-6884.

[12] Niu L F, Xin Y C, Wang R L, *et al*. Asymmetric *aza-Friedel-Crafts* reaction of 2-naphthol with tosylimines catalyzed by a dinuclear zinc complex [J]. *Synlett*, 2010, **5**:765-768.

[13] Liu G X, Zhang S L, Li H, *et al*. Organocatalytic enantioselective friedel-crafts reactions of 1-naphthols with aldimines[J]. *Org Lett*, 2011, **13**: 828-831.

[14] Cheng L, Liu L, Jia H, *et al*. Enantioselective organocatalytic *anti*-mannich-type reaction of *N*- unprotected 3-substituted 2-oxindoles with aromatic *N*-Ts-aldimines [J]. *J Org Chem*, 2009, **74**: 4650-4653.

[15] Jia Y X, Xie J H, Duan H F, *et al*. Asymmetric friedel-crafts addition of indoles to *N*-sulfonyl aldimines: a simple approach to optically active 3-indolyl-methanamine derivatives[J]. *Org Lett*, 2006, **8**: 1621-1624.

[16] Zhang T Y, He W, Zhao X Y, *et al*. Asymmetric oxaziridination catalyzed by *Cinchona* alkaloid derivatives containing sulfide[J]. *Tetrahedron*, 2013, **69**: 7416-7422.

Cinchona Alkaloid Derivatives Catalyzed Asymmetric *aza-Friedel-Crafts* Reaction of β-Naphthol with Tosylimines

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Abstract: *Cinchona* alkaloid derivatives as organocatalysts were applied in asymmetric *aza-Friedel-Crafts* reaction of β-naphthol with aryl aldimines. to synthesize Betti base derivatives. The effect of solvent, temperature and catalyst loading ammount were investigated. The optimized conditions were confirmed to include toluene as the solvent with a 10% loading of catalyst **1c** at 0 ℃. The products were obtained in 70% ~86% yield with up to 80% ee.

Key words: *cinchona* alkaloid derivative; asymmetric catalysis; *aza-Friede-Crafts* reaction; β-naphthol; betti base