靛红 Morita-Baylis-Hillman 碳酸酯与环状 *N*-磺酰亚胺的 不对称烯丙基烷基化反应研究

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摘要 本课题组近年来发展的通过路易斯碱催化靛红 Morita-Baylis-Hillman(MBH)碳酸酯的烯丙基烷基化反应是合成光学纯 3,3-二取代 2-氧化吲哚化合物的一种有效方法. 在此基础上, 本文研究了手性叔胺催化靛红 MBH 碳酸酯与环状 *N*-磺酰亚胺的不对称烯丙基烷基化反应, 通过亲电反应途径以较高的立体选择性(达 86% *ee*, *dr* > 95 : 5)和高收率(达 96%)合成 C-3 位含季碳手性中心的多官能团氧化吲哚产物. 通过简单的转化可以得到含多个手性中心的 2-吲哚酮-3,4'-哌啶环类骨架, 这为进一步合成生理活性物质研究奠定了基础.

关键词 不对称有机催化; 烯丙基烷基化; Morita-Baylis-Hillman 碳酸酯; 环状 *N*-磺酰亚胺; 2-氧化吲哚; 季碳手性中心; 2-吲哚酮-3,4'-哌啶环

Asymmetric Allylic Alkylation of Cyclic *N*-Sulfonylimines with Morita-Baylis-Hillman Carbonates of Isatins

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Abstract Enantiomerically pure 3,3-disubstituted 2-oxindoles are important building blocks for the synthesis of diverse oxindoles which are the core structure of many natural products and biologically active compounds. A number of asymmetric reactions to access such chiral materials have been reported over the past years, most of which rely on the application of nucleophilic 3-substituted oxindoles. Although these methods have been proved to be useful, some challenging issues still remain in terms of efficiency, stereoselectivity and substrate scope. On the other hand, recently, we have developed some highly stereoselective allylic alkylation reactions with Morita-Baylis-Hillman (MBH) carbonates of isatins and diverse nucleophiles, to produce 3,3-disubstituted oxindoles under the catalysis of metal-free Lewis basic tertiary amines. In this work, the first asymmetric assembly of MBH carbonates of isatins and cyclic *N*-sulfonylimines is reported. An array of tertiary amine catalysts derived from β -isocupreidine (β -ICD) and a variety of reaction parameters have been systematically investigated, and the optimized conditions were determined to run the reaction at $-20\text{ }^{\circ}\text{C}$ using PhCF_3 as the solvent, 4 Å MS as the additive, in the presence of 10 mol% of amine catalyst **1h**. A number of MBH carbonates **2** derived from diversely substituted isatins and cyclic *N*-sulfonylimines **3** could be well tolerated under the established catalytic conditions, providing an alternative electrophilic pathway to access multifunctional oxindoles bearing adjacent quaternary and tertiary stereogenic centers (up to 86% *ee*, *dr* > 95 : 5) in high yield (up to 96%). Moreover, the thus obtained chiral 3,3-disubstituted 2-oxindole could be used for the synthesis of complex spirocyclic 2-oxindole-3,4'-piperidine product. In this case, the chemoselective reduction of imine group of allylic alkylation product **4a** has been realized by using NaBH_4 as the reducing reagent at $-20\text{ }^{\circ}\text{C}$. A following intramolecular aza-Michael addition reaction gave a 2-oxindole-3,4'-piperidine product **6** in a moderate yield.

Keywords asymmetric organocatalysis; allylic alkylation; Morita-Baylis-Hillman carbonates; cyclic *N*-sulfonylimines; 2-oxindoles; quaternary chiral centre; 2-oxindole-3,4'-piperidine

1 引言

通过不对称方法构建季碳中心一直是有机合成中的一个挑战^[1]. 其中, 在氧化吲哚 3 位实现不对称的螺环骨架构建更吸引了化学工作者的极大兴趣^[2]. 同时,

由于 2-吲哚酮-3,4'-哌啶环类骨架在天然产物及药物活性物质中广泛存在, 其光学纯化合物也因其特殊的生理活性而受到关注(图 1). 但是, 2-吲哚酮-3,4'-哌啶环类骨架的不对称合成方法却少有报道.

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图1 代表性含2-吲哚酮-3,4'-吡啶环类骨架的天然产物

Figure 1 Represented nature products containing 2-oxindole-3,4'-pyridine core structure

氧化吲哚3位的不对称反应多通过3位取代2-氧化吲哚对多种亲电试剂的亲核加成反应来实现, 在过去几年中有大量文献报道^[3]. 最近, 本课题组发展了手性路易斯碱, 如 β -isocupreidine (β -ICD)及其衍生物^[4], 催化靛红 Morita-Baylis-Hillman(MBH)碳酸酯的烯丙基烷基化反应, 能高效合成 3,3-二取代氧化吲哚化合物^[5,6]. 但是, 手性产物结构的多样性仍然受制于底物类型以及催化剂的活性等.

最近, 我们发现环状 *N*-磺酰亚胺的 α -C—H 具有较强的酸性, 可以在温和条件下作为亲核试剂实现不对称 C—C 键的形成^[7]. 因此, 该类化合物与靛红 MBH 碳酸酯的不对称反应则可以顺利构建具有多官能团的手性氧化吲哚化合物, 并可进一步衍生得到更复杂的产物. 下面将报道该反应的具体研究结果.

2 结果与讨论

2.1 溶剂、催化剂、底物结构及温度对反应对映选择性的影响

我们首先尝试了 β -ICD 衍生物 **1a** 催化靛红 MBH 碳酸酯 **2a** 与环状 *N*-磺酰亚胺 **3a** 的反应, 发现该反应在 5 °C 下于甲苯中经过 20 h 便能以高收率得到单一目标产物 **4a**, 但仅有较低的对映选择性(Table 1, Entry 1). 因此, 我们首先对溶剂进行了筛选(Entries 2~6), 发现在三氟甲苯中能够得到 63% *ee* (Entry 6). 随后, 我们对 MBH 底物结构进行了修饰(**2b**~**2e**), 但都给出了较差的反应结果(Entries 7~10). 在此基础上, 我们进一步考察了多种修饰的 β -ICD 催化剂 **1b**~**1h** (Entries 11~17), 发现含对三氟甲基苯基取代的催化剂 **1h** 能实现更好的手性控制(Entry 17). 降低反应温度能略微提升对映选择性(Entry 18), 但反应明显变慢; 幸运的是添加 4 Å 分子筛能显著提高收率并有利于获得更好的对映选择性

(Entry 19).

表1 反应条件筛选

Table 1 Screening studies on reaction conditions^a

Entry	1	2	Solvent	<i>t</i> /h	Yield ^b /%	<i>ee</i> ^c /%
1	1a	2a	Toluene	20	4a, 80	29
2	1a	2a	MeCN	15	4a, 71	58
3	1a	2a	THF	18	4a, 75	22
4	1a	2a	CHCl ₃	18	4a, 93	61
5	1a	2a	DCE	12	4a, 93	43
6	1a	2a	PhCF ₃	20	4a, 97	63
7	1a	2b	PhCF ₃	17	4b, 99	49
8	1a	2c	PhCF ₃	18	4c, 26	14
9	1a	2d	PhCF ₃	17	4d, 99	54
10	1a	2e	PhCF ₃	16	4e, 22	22
11	1b	2a	PhCF ₃	12	4a, 84	71
12	1c	2a	PhCF ₃	14	4a, 99	60
13	1d	2a	PhCF ₃	18	4a, 71	43
14	1e	2a	PhCF ₃	12	4a, 88	8
15	1f	2a	PhCF ₃	12	4a, 84	11
16	1g	2a	PhCF ₃	18	4a, 62	64
17	1h	2a	PhCF ₃	12	4a, 99	76
18 ^d	1h	2a	PhCF ₃	70	4a, 62	77
19 ^{d,e}	1h	2a	PhCF ₃	72	4a, 88	79

^a Unless otherwise noted, reactions were performed with MBH carbonate **2** (0.1 mmol), cyclic *N*-sulfonylimines **3a** (0.12 mmol), catalyst **1** (0.01 mmol) in solvent (1.0 mL) at 5 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis; *dr* > 95 : 5. ^d At -20 °C. ^e 4 Å MS (10 mg) was added.

2.2 底物普适性

通过以上条件筛选, 我们确定使用 10 mol % 手性催化剂 **1h**, PhCF₃ 为溶剂, 在 -20 °C 条件下添加 4 Å 分子筛考察反应底物普适性, 实验结果见表 2. 我们首先研究了靛红 MBH 碳酸酯 **2a** 与含不同侧链取代环状 *N*-磺酰亚胺的反应情况, 以较好的收率(71%~94%)和较高的对映选择性(77%~84% *ee*)得到相应的目标产物, 而反应的非对映选择性都很好(Table 2, Entries 1~6). 其次, 考察了环状 *N*-磺酰亚胺 **3a** 与多种取代靛红 MBH 碳酸酯的反应情况. 结果表明, 无论是含有给电子基团或者吸电子基团(Entries 7~15), 大部分底物均能得到较好的收率(69%~96%)和较高的对映选择性(73%~86% *ee*), 但 5-碘和 5,7-二甲基取代的 MBH 碳酸酯由于副产物的生成以及转化不完全, 给出较低收率(Entries 9 and 15). 另外, 由于所得到的烯丙基取代产物多为固体, 通

过简单的重结晶即可得到几乎光学纯的产物(Entries 1 and 8 括号中数据).

表 2 底物普适性考察

Table 2 Studies on substrate scope and limitations^a

Entry	R	R ¹	t/h	Yield ^b /%	ee ^c /%
1	H	<i>n</i> -Pr	72	4a , 88 (69 ^d)	79 (99 ^d)
2	H	Me	72	4f , 73	82
3	H	PhCH ₂ CH ₂	71	4g , 72	84
4	H	Et	72	4h , 94	77
5	H	<i>n</i> -Bu	76	4i , 89	82
6	H	<i>i</i> -Bu	70	4j , 71	77
7	5-Me	<i>n</i> -Pr	84	4k , 69	77
8	5-MeO	<i>n</i> -Pr	93	4l , 85 (59 ^d)	75 (99 ^d)
9	5,7-Me ₂	<i>n</i> -Pr	99	4m , 46	72
10	5-CF ₃ O	<i>n</i> -Pr	79	4n , 95	75
11	5-F	<i>n</i> -Pr	75	4o , 85	86
12	7-F	<i>n</i> -Pr	93	4p , 77	83
13	5-Cl	<i>n</i> -Pr	76	4q , 72	73
14	5-Br	<i>n</i> -Pr	76	4r , 96	75
15	5-I	<i>n</i> -Pr	96	4s , 51	75

^a Unless otherwise noted, reactions were performed with MBH carbonate **2** (0.1 mmol), cyclic *N*-sulfonylimines **3** (0.12 mmol), catalyst **1h** (0.01 mmol) in PhCF₃ (1 mL) at -20 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis; *dr* > 95 : 5. ^d Data in parentheses were obtained after recrystallization.

我们从化合物 **4l** 的乙酸乙酯和正己烷溶液中得到其单晶结构, 从而可以顺利确定产物的绝对构型, 其结构见图 2^[8].

图 2 光学纯化合物 **4l** 的单晶结构

Figure 2 X-ray structure of enantiopure **4l**

2.3 2-吲哚酮-3,4'-哌啶环类骨架产品的合成研究

我们进一步尝试了 2-吲哚酮-3,4'-哌啶环类骨架的合成. 在 -20 °C 条件下, 硼氢化钠可以选择性还原烯丙基取代产物 **4a** 的亚胺官能团, 并获得很好的非对映选择性. 随后在 NaOH 和相转移催化剂四丁基溴化铵 (TBAB) 存在下, 中间体 **5** 发生分子内氮杂 Michael 加成反应, 以较好的收率和非对映选择性得到含多手性中心的 2-吲哚酮-3,4'-哌啶环类骨架产物 **6** (见图式 1).

图式 1 2-吲哚酮-3,4'-哌啶环类骨架的合成

Scheme 1 Synthesis of 2-oxindole-3,4'-piperidine product

3 结论

我们研究了靛红 MBH 碳酸酯与环状 *N*-磺酰亚胺的不对称烯丙基化反应. 利用修饰的 β -ICD 衍生物 **1h** 作为催化剂, 在氧化吲哚 3 位成功构建了手性季碳中心, 以较高对映选择性 (达 86% *ee*) 和很好的非对映选择性 (> 95 : 5) 获得了多官能团氧化吲哚产物, 并通过重结晶可得到光学纯的手性产物. 通过进一步的化学转化, 可得到含多手性中心的 2-吲哚酮-3,4'-哌啶环类骨架, 这为进一步设计合成生理活性物质奠定了基础^[9].

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