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Chiral Bicycle Imidazole Nucleophilic Catalysts: Rational Design, Facile Synthesis, and Successful Application in Asymmetric Steglich Rearrangement

Zhenfeng Zhang, Fang Xie, Jia Jia, and Wanbin Zhang*

School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China

Received October 8, 2010; E-mail: wanbin@sjtu.edu.cn

Abstract: A new type of chiral bicycle imidazole nucleophilic catalyst was rationally designed, facilely synthesized, and successfully applied in an asymmetric Steglich rearrangement with good to excellent yield and enantioselectivity at ambient temperature. Moreover, it can be easily recycled with almost no reduction of catalytic efficiency. This is the first example for the successful chiral imidazole nucleophilic catalyst without H-bonding assistance.

In recent years, a number of chiral nonenzymatic nucleophilic catalysts have been introduced for enantioselective acyl transfer and offered useful levels of enantioselectivity in kinetic resolution (KR), asymmetric desymmetrization (AD), and related transformations.[1] For asymmetric Steglich rearrangement of *O*-acylated azlactones to their *C*-acylated isomers,[2−6] which is one of a few methods for producing a quaternary stereocenter,[7] Fu's planar-chiral 4-dimethylamino-pyridine (DMAP) catalyst,[2] Vedejs' chiral phosphine catalyst and central chiral DMAP catalyst,[3] and Birman's amidine catalyst[4] served as the most efficient ones. However, there are still some limitations for practical applications of these catalysts, such as expensive reagents and multistep sequences in their synthesis and/or harsh conditions in asymmetric catalysis. Developing new classes of chiral nucleophilic catalysts remains an important challenge.

N-Methylimidazole (NMI), which bears an electron-donating sp^2-N atom and a π-electron conjugated system, has already been proven to be a good nucleophilic catalyst,[8] but only a few types of chiral NMI nucleophilic catalysts were reported[9,10] compared with chiral pyridine and amidine nucleophilic catalysts. Moreover, their stereocontrol groups are mostly placed at the 5-position of imidazole,[9] which makes it difficult to control the chiral environment due to the far distance away from the nucleophilic sp^2-N atom. Therefore, a secondary interaction such as H-bonding is essential for these catalysts to improve enantioselectivity, which results in the limitation of the application scope.

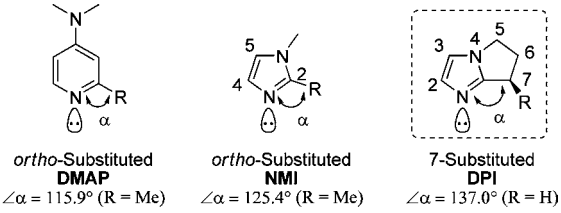
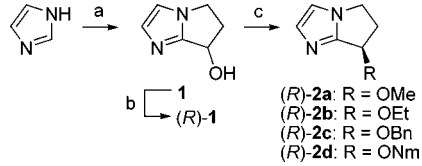


Figure 1. Design of Catalyst **DPI**.

As far as we know, only one type of *ortho*-substituted chiral DMAP nucleophilic catalyst was reported[11] because of the low activity of this kind of catalyst caused by steric hindrance from the *ortho* stereocontrol group.[12] Although the activity of the *ortho*-substituted chiral NMI nucleophilic catalyst is higher[10] due to its larger ∠α than that of *ortho*-substituted chiral DMAP,[13] it is still unsatisfactory for some reactions with bulky substrates and reagents (Figure 1).[14] In order to reduce or even avoid the *ortho* group's influence to activity, we designed a rigid bicyclic structure of 6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole (abbreviated as **DPI**) with a much larger ∠α as the skeleton of our catalysts (Figure 1). Therefore, good stereocontrol would be expected since the stereocontrol group R designed at the 7-position of **DPI** is nearby to the catalytic active site and allowed to be efficiently adjustable. Here we want to describe the first successful result regarding its synthesis and application in asymmetric Steglich rearrangement.

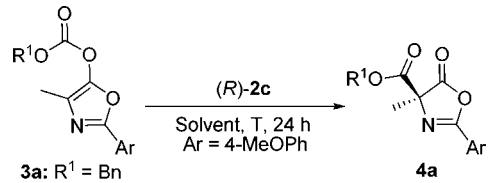
Scheme 1. Synthesis of (*R*)-**2**[a]



[a] Conditions: (a) acrolein, AcOH, dioxane, reflux, 81%; (b) (+)-tartaric acid, MeOH, 11% (99.9% ee), or preparative HPLC, 47% (99.9% ee); (c) (*R*)-**2a**: NaH, THF, rt; then MeI, rt, 42%; (*R*)-**2b**: NaH, THF, rt; then EtBr, reflux, 91%; (*R*)-**2c**: NaH, THF, rt; then BnBr, reflux, 73%; (*R*)-**2d**: NaH, DMF, rt; then 1-chloromethyl naphthalene (NmCl), rt, 54%.

The catalysts were synthesized from facile starting materials of imidazole and acrolein with ease in three steps (Scheme 1). First, the key intermediate **1** was obtained in 81% yield with a modification of the literature procedure.[15] Then, the enantiomers of **1** were

Table 1. Optimization Studies[a]



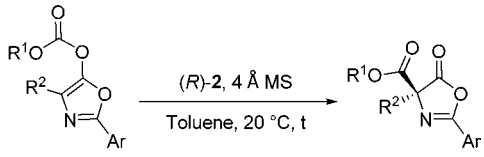
Entry	Substrate	Solvent	*T* (°C)	Yield (%)[b]	Ee (%)[c]
1	**3a**	MeCN	20	38	74
2	**3a**	DCM	20	60	83
3	**3a**	*t*-AA	20	33	71
4	**3a**	THF	20	30	88
5	**3a**	Et_2O	20	31	92
6	**3a**	Toluene	20	30	93
7	**3a**	Hexane	20	12	69
8[d]	**3a**	Toluene	20	29	93
9[e]	**3a**	Toluene	20	29	94
10[e,f]	**3a**	Toluene	0	14	94
11[e]	**3a**	Toluene	40	52	91
12[e]	**3b**	Toluene	20	68	86
13[e]	**3c**	Toluene	20	46	98

[a] Conditions: 0.05 M **3**, 10 mol % (*R*)-**2c**, 1.0 mL of solvent, 24 h. [b] Yields are calculated from ^{1}H NMR spectroscopy. [c] Ee's are determined by HPLC analysis. [d] The concentration of **3a** is 0.10 M. [e] Addition of 4 Å MS. [f] The reaction time is 48 h.

separated by optical resolution or preparative HPLC and simply derived to give (*R*)-**2** in high yields.[16]

Then, (*R*)-**2** was applied in the asymmetric Steglich rearrangement of *O*-acylated azlactones to their *C*-acylated isomers. Initial study on the solvent effect showed that low-polar solvents gave higher ee's but lower yields in the asymmetric rearrangement of **3a** (Table 1, entries 1−7). Toluene as the preferred solvent gave the highest ee (entry 6), but hexane gave the lowest ee probably due to its poor solubility for both catalyst and substrate (entry 7). To further improve the yield and ee, we optimized the reaction conditions. First, we increased the concentration of **3a** from 0.05 to 0.10 M, but there was almost no effect (entry 8 vs 6). Then, we found that the addition of a 4 Å molecular sieve could slightly improve the ee (entry 9 vs 6). And raising the reaction temperature could increase the yield but decrease the ee (entries 9−11). A great increase of yield was observed by changing R^1 from Bn to Ph, though the ee dropped to 86% (entry 12). And the highest ee of 98% was achieved when R^1 was changed to be CMe_2CCl_3 (entry 13).

Table 2. Interaction between Catalysts and Substrates[a]



3a: Ar = 4-MeOPh, R^1 = Bn, R^2 = Me **4a**
3d: Ar = Ph, R^1 = Bn, R^2 = Me **4d**
3e: Ar = 4-MeOPh, R^1 = Bn, R^2 = Et **4e**
3f: Ar = 4-MeOPh, R^1 = Bn, R^2 = $CH_2CH_2SCH_3$ **4f**
3g: Ar = 4-MeOPh, R^1 = Bn, R^2 = Bn **4g**
3h: Ar = 4-MeOPh, R^1 = Bn, R^2 = *i*-Bu **4h**
3i: Ar = 4-MeOPh, R^1 = Bn, R^2 = *i*-Pr **4i**
3j: Ar = 4-MeOPh, R^1 = Ph, R^2 = *i*-Pr **4j**
3k: Ar = 4-MeOPh, R^1 = Bn, R^2 = Ph **4k**

Entry	Substrate	Catalyst	*t* (d)	Yield (%)[b]	Ee (%)[c]
1	**3a**	(*R*)-**2a**	1	18	90
2	**3a**	(*R*)-**2b**	1	21	91
3	**3a**	(*R*)-**2c**	1	29	94
4	**3a**	(*R*)-**2d**	1	26	95
5[d]	**3a**	(*R*)-**2c**	1	17	93
6[e]	**3a**	(*R*)-**2c**	1	39	94
7	**3a**	(*R*)-**2c**	4	75	94
8	**3a**	(*R*)-**2c**	6	81	95
9	**3a**	(*R*)-**2d**	6	83	95
10	**3d**	(*R*)-**2c**	6	96	94
11	**3d**	(*R*)-**2d**	6	96	93
12	**3e**	(*R*)-**2c**	6	61	94
13	**3e**	(*R*)-**2d**	6	63	93
14	**3f**	(*R*)-**2c**	6	94	95
15	**3f**	(*R*)-**2d**	6	93	93
16	**3g**	(*R*)-**2c**	6	93	93
17	**3g**	(*R*)-**2d**	6	96	93
18	**3h**	(*R*)-**2c**	6	50	95
19	**3h**	(*R*)-**2d**	6	58	87
20[f]	**3i**	(*R*)-**2c**	6	35	84
21[f]	**3j**	(*R*)-**2c**	6	75	78
22	**3k**	(*R*)-**2c**	6	99	59
23	**3k**	(*R*)-**2d**	6	99	58

[a] Conditions: 0.05 M **3**, 10 mol % (*R*)-**2**, 1.0 mL of toluene, 20 °C. [b] Yields are calculated from ^{1}H NMR spectroscopy. [c] Ee's are determined by HPLC analysis. [d] The loading of catalyst is 5 mol %. [e] The loading of catalyst is 20 mol %. [f] The reaction temperature is 75 °C.

Further studies on the interaction between catalysts and substrates showed that (*R*)-**2c** and (*R*)-**2d** were the most effective catalysts for the rearrangement of **3a** to **4a** (Table 2, entries 1−4). And a higher yield and ee could be achieved by increasing the loading of catalyst (entries 3, 5, 6) or extending the reaction time (entries 3, 7, 8). Using (*R*)-**2c** and (*R*)-**2d** as the optimized catalysts, the six primary alkyl-substituted substrates **3a** and **3d**−**h** at C4 were asymmetrically rearranged to corresponding products at 20 °C with excellent yields and ee's (entries 8−19). Remarkably, the most commonly used substrate **3a** was rearranged by (*R*)-**2c** with 95% ee (entry 8), which is the best result to the best of our knowledge.[2−5] Additionally, these catalysts were also effective for secondary alkyl- and aryl-substituted substrates **3i**−**k** (entries 20−23).

Lastly, we examined the possibility of catalyst recycling and found that this kind of nucleophilic catalyst could be easily recovered and reused in this rearrangement reaction five times with little loss in quantity and almost no reduction of catalytic efficiency (for details please see Supporting Information).

In conclusion, a new type of chiral bicycle imidazole nucleophilic catalyst (*R*)-**2** was rationally designed, facilely synthesized, and successfully applied in an asymmetric Steglich rearrangement with good to excellent yield and enantioselectivity at ambient temperature. Moreover, it can be easily recycled with almost no reduction of catalytic efficiency. This is the first example of a successful chiral imidazole nucleophilic catalyst without H-bonding assistance. Further studies on its application in other reactions are underway.

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Supporting Information Available: Experimental procedures, spectroscopic data, chromatographic data and crystallographic data of (*R*)-**1** (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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