Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202001128

Link to VoR: https://doi.org/10.1002/adsc.202001128

10.1002/adsc.202001128

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Catalytic Enantioselective Synthesis of *N*,*N*-Acetals from α-Dicarbonyl Compounds Using Chiral Imidazoline-Phosphoric Acid Catalysts

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The enantioselective synthesis of chiral *N*,*N*-acetals derived from α-dicarbonyl compounds has been achieved. Good yields and enantioselectivities were observed for the reaction with various α-dicarbonyl compounds with 2-aminobenzamides using chiral bis(imidazoline)-phosphoric acid catalysts. Based on these experimental investigations, a possible transition state is proposed to explain the origin of the asymmetric induction.

Keywords: Enantioselectivity; *N*,*N*-Acetals; Imidazoline; Organic catalysis, Ketimines

The family of chiral *N*,*N*-acetals and their derivatives includes important compounds that are pharmacologically active, such as bendroflumethiazide,[1] thiabutazide,[2] palcernuine,[3] baloxavir marboxil,[4] physostigmine,[5] and saxitoxine,[6] as well as chiral catalysts or chiral auxiliary (Figure 1).[7] Furthermore, 2,3-dihydroquinazolinone backbones, such as aquamox, are important structure motifs in compounds that also exhibit bioactivities, such as antitumor, analgesic, antifibrillatory, antibiotic, antispermatogenic, and vasodilatory efficacy.[2,8] In addition, the enantiomers of some 2,3-dihydroquinazolinone compounds show different bioactivities.[8h,9]

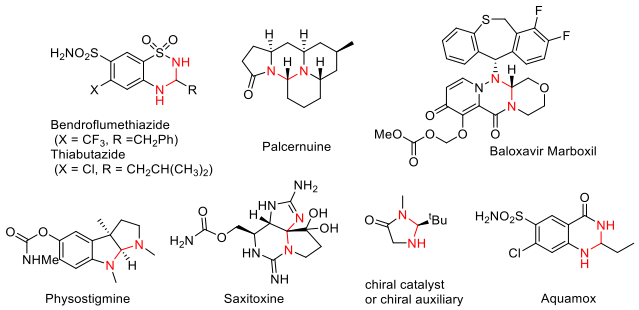

Figure 1. Examples of biologically active *N*,*N*-acetals

Their broad utility has prompted considerable interest to develop asymmetric methods for their preparation. Therefore, there are several reports on the enantioselective synthesis of chiral *N*,*N*-acetals prepared from aldehydes,[10] aldimines[11,12] or enamines.[13] However, the electrophilic substrates in enantioselective *N*,*N*-acetal formation reactions were mainly restricted to aldehyde or imines, but the enantioselective reaction using ketones is still not fruitful. The first enantioselective *N*,*N*-acetal formation reaction with ketones was reported by List and co-workers, who used isatin, as a ketone, together with 2-aminobenzamide to give spirodihydroquinazolinone with 84% ee.[10a] After this pioneering work, enantioselective *N*,*N*-acetal syntheses of 2-aminobenzamide with isatins were reported by Shi[14] and Wang's groups.[15] Recently, Smith and co-workers reported the enantioselective intramolecular *N*,*N*-acetal formation of trifluoromethyl alkyl ketimines with a pyrrole moiety to give products with up to 98% ee.[16] The enantioselective reactions of 2*H*-azirine as a ketimine with pyrazole or indoline-2-one were reported by Zhang,[17] and Liu and Feng's group.[18] Wang and co-workers reported the enantioselective tandem cyclization of alkyne, amine, and indole using chiral phosphoric acid catalysts.[19] Lin and Duan[20] and Li and co-workers[21] independently reported the enantioselective formation of *N*,*N*-acetals between ketimines derived from isatins with amines or triazoles using chiral thiourea catalysts. The first highly enantioselective *N*,*N*-acetal formation reaction with acyclic ketones was reported by Zhou and co-workers, they examined the reaction of 2-(1*H*-indolyl)anilines and trifluoromethyl ketones.[22] On the other hand, we recently developed enantioselective C-O, C-S, and C-C bond formations to ketimines giving chiral *N*,*O*-acetals,[23] *N*,*S*-acetals[24] and amines having tetra-substituted carbon

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centers,[25] and novel chiral imidazoline-phosphoric acid catalysts.[26] Herein, our ongoing interest was extended to the catalytic *N*,*N*-acetal formation reaction of acyclic ketones with 2-aminobenzamide using chiral imidazoline-phosphoric acid catalysts (Figure 2).

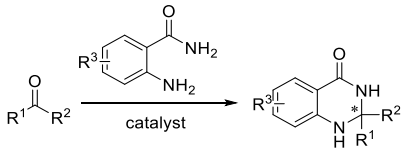
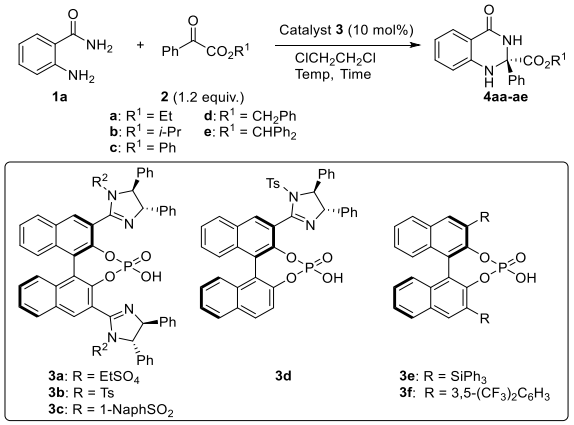


Figure 2. Enantioselective formation of *N*,*N*-acetals by the reaction of ketones with 2-aminobenzamides

We first examined the enantioselective reaction of 2-aminobenzamide **1a** (1.0 equiv.) with various α-ketoesters **2a-e** (1.2 equiv.) using 10 mol% of chiral phosphoric acid catalysts **3a-f**. The results are shown in Table 1. The reaction of **1a** with **2a** using chiral bis(imidazoline)-phosphoric acid catalyst **3a** proceeded to give product **4aa** in good yield albeit with low enantioselectivity (Table 1, entry 1). The enantioselectivity was improved by changing the substituent on nitrogen in imidazoline catalysts from an ethanesulfonyl group to a tosyl or a 1-naphthalenesulfonyl group (Table 1, entries 2 and 3). Mono-imidazoline-phosphoric acid catalyst **3d** showed low enantioselectivity (Table 1, entry 4). We also examined commercially available chiral phosphoric acid catalysts **3e**,**f** having triphenylsilyl or a 3,5-bis(trifluoromethyl)phenyl group to afford **4aa** with low enantioselectivity (Table 1, entries 5 and 6).[27] To improve enantioselectivity, we optimized the structure of α-ketoesters **2a-e** (Table 1, entries 7-10). As a result, the reaction using α-ketoester **2e** having a benzhydryl group gave product **4ae** with high enantioselectivity but in moderate yield (Table 1, entry 10). To our delight, the reaction using 3.0 equivalent of α-ketoester at a lower temperature improved the yield and enantioselectivity of the product (Table 1, entry 11).

Next, we examined the reaction of various aminobenzamides **1a-e** with α-ketoesters **2e-q** using catalyst **3c** (Table 2). The reaction of **2e** with **1b** having an electron-donating methyl group showed good enantioselectivity and yield of product (Table 2, entry 2). The reaction of **1c-e** bearing electron-

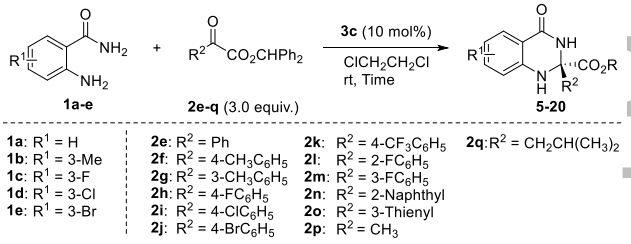
Table 1. Optimization of the reaction of various α-ketoesters **2a-e** with 2-aminobenzamide **1a** using chiral catalysts **3**[a)]



Entry	2	3	Temp (°C)	Time (h)	Yield (%)	Ee (%) [b)]
1	**2a**	**3a**	70	72	73	38
2	**2a**	**3b**	70	72	88	64
3	**2a**	**3c**	70	72	75	70
4	**2a**	**3d**	70	72	74	27
5	**2a**	**3e**	70	72	14	9
6	**2a**	**3f**	70	72	91	1
7	**2b**	**3c**	70	72	71	74
8	**2c**	**3c**	70	72	70	23
9	**2d**	**3c**	70	72	91	70
10	**2e**	**3c**	70	72	52	89
11 [c)]	**2e**	**3c**	rt	160	99	92

[a)] Reaction conditions: The reaction was carried out using **1a** (0.1 mmol), **2** (1.2 equiv.), and **3** (10 mol%) in 1,2-dichloroethane (0.1 M) at 70 °C. [b)] Enantiomer excess was determined by HPLC analysis using chiral column. [c)] **2e** (3.0 equiv.) was used.

Table 2. The reaction of various 2-aminobenzamides **1a-e** with various α-ketoesters **2e-q** using **3c**[a)]

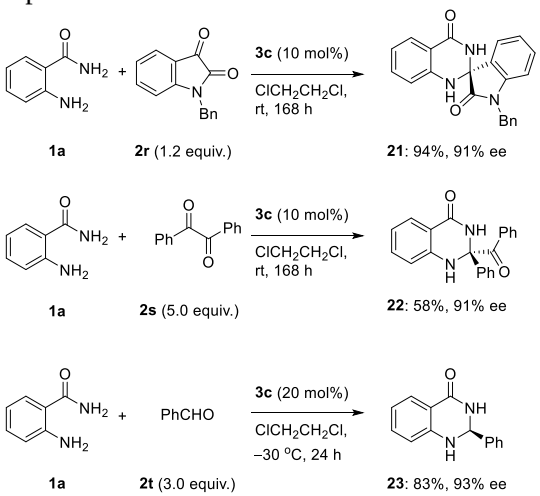


Entry	1	2	Product	Time (h)	Yield (%)	Ee (%) [b)]
1	**1a**	**2e**	**4ae**	160	99	92
2 [b)]	**1b**	**2e**	**5**	120	88	82
3 [b)]	**1c**	**2e**	**6**	120	84	96
4 [b)]	**1d**	**2e**	**7**	160	79	93
5 [b)]	**1e**	**2e**	**8**	240	77	95
6	**1a**	**2f**	**9**	140	90	93
7 [b)]	**1a**	**2g**	**10**	140	91	93
8 [b)]	**1a**	**2h**	**11**	140	93	91
9	**1a**	**2i**	**12**	140	77	92
10	**1a**	**2j**	**13**	140	87	92
11	**1a**	**2k**	**14**	210	81	93
12 [b,c)]	**1a**	**2l**	**15**	168	95	85
13 [b)]	**1a**	**2m**	**16**	190	88	86
14 [b)]	**1a**	**2n**	**17**	140	85	95
15 [b)]	**1a**	**2o**	**18**	90	77	93
16 [c,d)]	**1a**	**2p**	**19**	48	95	76
17 [b,c)]	**1a**	**2q**	**20**	15	88	89

[a)] Reaction conditions: The reaction was carried out using **1** (0.1 mmol), **2** (3.0 equiv.), and **3c** (10 mol%) in 1,2-dichloroethane (0.1 M) at rt. [b)] **2** (5.0 equiv.) was used. [c)] The reaction was carried out using 20 mol% of **3c**. [d)] The reaction was carried out at 0 °C.

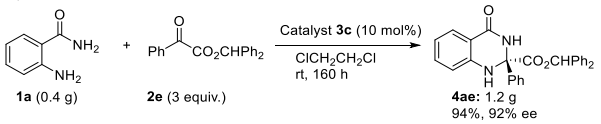
withdrawing groups, such as a fluoro, chloro, and bromo groups, also gave products **6**-**8** in high yield with high enantioselectivity (77-84%, 91-96% ee, Table 2, entries 3-5).[28] The reaction of **1a** with **2f**,**g** having a methyl group in the *meta* or *para* position gave products **9**,**10** in high yield with high enantioselectivity (93% ee, Table 2, entries 6 and 7). The reaction with **2h-m** bearing an electron-withdrawing group in *ortho*, *meta*, and *para* positions gave products **11**-**16** in high yield with high enantioselectivity (75-95%, 85-93% ee, Table 2, entries 8-13). 2-Naphthyl and 3-thienyl α-ketoesters **2n** and **2o** gave products **17**,**18** with high enantioselectivity (Table 2, entries 14 and 15). Furthermore, the reaction of alkyl-substituted α-ketoesters **2p** or **2q** with **1a** gave products **19**,**20** in good yield with high enantioselectivity (Table 2, entries 16 and 17).

We also examined the enantioselective synthesis of *N*,*N*-acetals by the reaction of *N*-benzyl isatin **2r** as a cyclic α-ketoamide compound, benzil **2s** as an acyclic diketone, or benzaldehyde **2t** with 2-aminobenzamide **1a**. The reaction using **3c** afforded products **21**-**23** in high yield with good enantioselectivity (91-93% ee, Scheme 1). The absolute stereochemistry of products **21** and **23** were determined to assigned to be S in comparison with the value of the specific rotation reported in the literature.[10d,14]



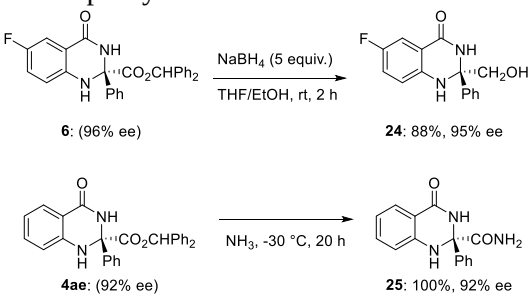
Scheme 1. Enantioselective reaction of *N*-benzylisatin **2r**, benzil **2s**, or benzaldehyde **2t** with 2-aminobenzamide **1a**

The gram-scale synthesis of *N*,*N*-acetal **4ae** via the reaction of 0.4 g of **1a** with **2e** using catalysts **3c** successfully proceed to afford 1.2 g of **4ae** (Scheme 2).



Scheme 2. Gram-scale synthesis of *N*,*N*-acetal **4ae** by the reaction of **1a** with **2e** using catalyst **3c**.

We next examined the transformation of *N*,*N*-acetals. Reduction of the ester group in product using sodium borohydride in THF/EtOH gave corresponding primary alcohol **24** in high yield (Scheme 3). The absolute configuration of **24** was determined as (*R*) by X-ray crystallographic analysis,[29] and the configuration of other products was tentatively assumed by analogy. The amidation of **4ae** in NH_3 afforded amide **25** in high yield without the loss of enantiopurity.



Scheme 3. Transformation of *N*,*N*-acetals to chiral alcohols **24** and amide **25**

The assumed catalytic cycle for the reaction of α-ketoesters **2** with aminobenzamides **1** is shown in Figure 3. Catalyst **3c** makes intramolecular hydrogen-bonding between phosphoric acid and imidazoline,[26] it activates α-ketoester **2** by a hydrogen-bonding interaction, then aminobenzamide **1** reacts to α-ketoester **2** to afford an *o*-iminobenzamide intermediate. The intramolecular nucleophilic addition of an amide group in *o*-iminobenzamide to the imine moiety gives chiral *N*,*N*-acetals. We checked the retro-*N*,*N*-acetal formation reaction of product **4ae** using catalyst **3c** and the cross- *N*,*N*-acetal formation reaction of product **4ae** with **1b** using **3c**. These reactions did not change the structure or enantiopurity of products. Therefore, the stereoselectivity of the reaction is kinetically controlled.

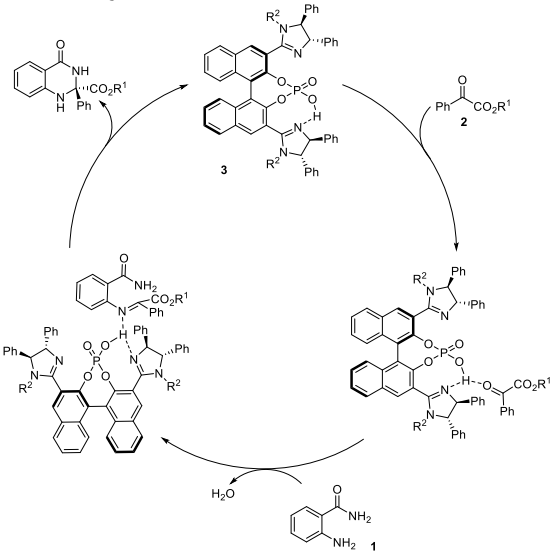


Figure 3. Proposed reaction cycle of the reaction of α-ketoesters **2** with 2-aminobenzamides **1** using catalyst **3**

Furthermore, we also examined the reaction of α-ketoester **2e** and 2-amino-*N*-methylbenzamide **1f**, but the reaction did not afford any product (Scheme 4). This result implies the importance of the activation of the intermediate imine with a chiral phosphoric acid catalyst.

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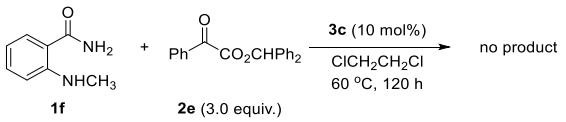

Scheme 4. Reaction of 2-amino-*N*-methylbenzamide **1f** with α-ketoester **2e** using catalyst **3c**

The assumed transition state for the enantioselective reaction of α-ketoester **2e** with 2-aminobenzamide **1a** using catalyst **3c** is shown in Figure 4. The reaction of **2e** with **1a** gave the ketimine intermediate, then catalyst **3c** enhances the electrophilicity of ketimine by hydrogen bondings. The amide group in the intermediate attacks the *Re*-face of ketimine intramolecularly, thus avoiding steric repulsion between the phenyl group on imidazoline, to afford the (*R*)-isomer of the product with high enantioselectivity. Further studies are required to fully elucidate the mechanistic detail of the *N*,*N*-acetal formation reaction.

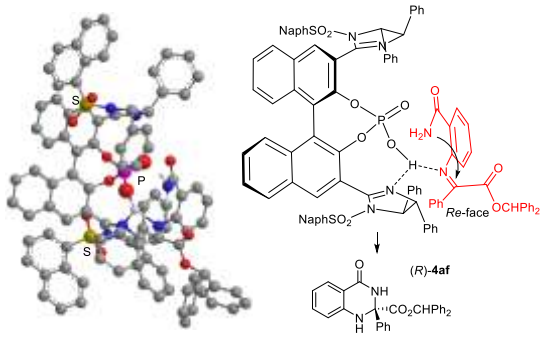

Figure 4. Assumed transition state for the reaction of **2e** with **1a** using catalyst **3c**. H atoms have been omitted for clarity.

In conclusion, we developed the highly enantioselective synthesis of *N*,*N*-acetals derived from α-dicarbonyl compounds and 2-aminobenzamides using chiral bis(imidazoline)-phosphoric acids catalysts. Various α-ketoesters and 2-aminobenzamides can be applied in the process. Further studies are in progress to the synthesize chiral cyclic compounds having a tetra-substituted carbon center.

Experimental Section

2-Aminobenzamide **1a** (13.6 mg, 0.1 mmol) was added to a solution of bis(imidazoline)-phosphoric acid catalyst **3c** (11.7 mg, 10 mol%) and α-ketoester **2e** (94.9 mg, 0.3 mmol) in dichloroethane (1.0 mL) at r.t. After stirred for 160 h, the mixture was purified over silica gel column chromatography (hexane/ethyl acetate=70:30) to give **4ae** (43.2 mg, 99%, 92% ee).

Acknowledgements

This work was supported by the Takahashi Industrial and Economic Research Foundation and the Astellas Foundation for Research on Metabolic Disorders.

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[29] CCDC 1980902 contains the crystallographic data for compound **12a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

10.1002/adsc.202001128

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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