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Remarkable Reaction Rate and Excellent Enantioselective Direct α-Amination of Aldehydes with Azodicarboxylates Catalyzed by Pyrrolidinylcamphor-Derived Organocatalysts

Pang-Min Liu,[a] Chihliang Chang,[a] Raju Jannapu Reddy,[a] Ying-Fang Ting,[a] Hsuan-Hao Kuan,[a] and Kwunmin Chen*[a]

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Remarkable reaction rate and excellent enantioselective direct α-amination of unmodified aldehydes with various azodicarboxylates was catalyzed by pyrrolidinylcamphor organocatalyst **2a** (5 mol-%) to provide the desired aminated products with excellent chemical yields and high to excellent levels of enantioselectivity (up to >99 % *ee*) at 0 °C in CH_2Cl_2.

Introduction

The formation of carbon–nitrogen bonds has received considerable attention in recent years, as nitrogen-containing molecules are potentially important building blocks.[1] Diastereoselective electrophilic amination of metal enolates with azodicarboxylates as the nitrogen source has been developed for the synthesis of α-hydrazino acids and α-amino acids with high levels of diastereoselectivity.[2] The metal-mediated catalytic enantioselective α-amination of 1,3-dicarbonyls,[3] keto esters,[4] and metal enolates/enolsilanes[5] with azodicarboxylates has recently been realized. In contrast, the efficient organocatalytic α-amination of α-substituted α-cyanoacetates, 1,3-dicarbonyls, or β-keto esters with azodicarboxylates has been documented, which leads to the synthesis of α-aminated products.[6] Asymmetric organocatalysis has recently attracted much attention due to the fact that organocatalysts are typically nontoxic, highly efficient, environmentally friendly, and stable under both aerobic and aqueous reaction conditions.[7] Recently, methods have been developed for the direct organocatalytic α-amination of unmodified aldehydes/ketones with azodicarboxylates.[8]

Since the ingenious work of List[8a] and Jørgensen,[8b] L-proline-catalyzed α-amination of aldehydes with azodicarboxylates has been shown to produce the corresponding products in high chemical yields and excellent enantioselectivities. In addition, the amination of α,α-disubstituted aldehydes with azodicarboxylate catalyzed by a variety of organocatalysts have been reported.[8e,8g,8h,8m,8n] However, the reactions generally require high catalyst loading (50 mol-%) under thermal or microwave-assisted conditions and resulted in moderate to good chemical yields and enantioselectivities.[8m,8n] Despite the excellent results achieved by several research groups, the development of an efficient method for the direct organocatalytic α-amination of aldehydes to azodicarboxylates with low catalyst loadings and shorter reaction time remains a challenging task in asymmetric synthesis.

Although many practical organocatalysts have been developed, only relatively few are effective with low catalyst loadings (5 mol-%).[9] We have recently designed and synthesized a series of novel pyrrolidinylcamphor-based organocatalysts for asymmetric organocatalysis.[10] In our continuous efforts toward developing new organocatalysts, we envision that the assembly of a well-defined structural camphor scaffold with a pyrrolidinyl motif linked with appropriate functionalities, such as, sulfides (**1a**–**f**), sulfones (**2a** and **2b**), sulfonamides (**3a** and **3b**), and amide (**4**), would act as efficient bifunctional organocatalysts in asymmetric synthesis (Scheme 1). We wish to report here an excellent enantioselective direct α-amination of aldehydes with various azodicarboxylates catalyzed by pyrrolidinylcamphor bifunctional organocatalysts. The desired α-aminated alcohols were obtained with high chemical yields and excellent enantioselectivities at 0 °C in 5–10 min with only 5 mol-% of organocatalyst **2a**.

[a] Department of Chemistry,
National Taiwan Normal University,
Taipei, Taiwan 116, ROC
Fax: +886-2-29324249
E-mail: kchen@ntnu.edu.tw

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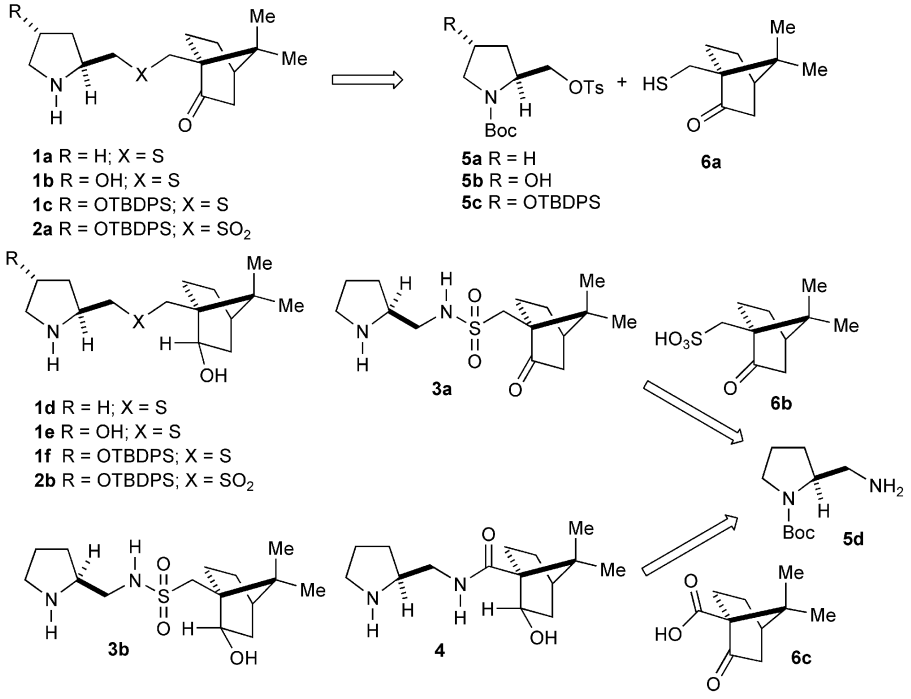


Scheme 1. Chemical structures of pyrrolidinylcamphor catalysts **1**–**4**.

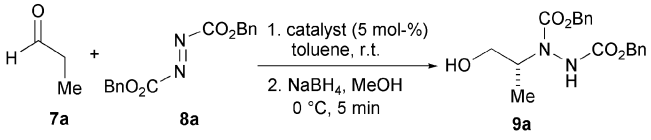
Results and Discussion

The synthesis of organocatalysts **1**–**4** began with known *N*-Boc protected L-proline analogues **5a**–**d** and camphor derivatives **6a**–**c** (Scheme 1). Organocatalysts **1a**–**c** were obtained by the reaction of *N*-Boc *O*-tosylated prolinol derivatives **5a**–**c** with 1-mercaptomethyl-7,7-dimethylbicyclo-[2.2.1]heptan-2-one (**6a**) in the presence of NaH, followed by Boc deprotection with trifluoroacetic acid (TFA). The $NaBH_4$ reduction of *N*-Boc **1a**–**c** provided the corresponding *exo*-alcohol (C2-camphor numbering) as a single diastereomer, which was treated with TFA in CH_2Cl_2 to generate desired organocatalysts **1d**–**f** without any incident. Desired sulfone-linked organocatalyst **2a** was obtained by the oxidation of *N*-Boc **1c** with Oxone under basic conditions. The removal of the Boc group was performed after the reduction step to afford the corresponding *exo*-alcohol organocatalyst **2b** as a single diastereomer.

In contrast, sulfonamide organocatalysts **3a** and **3b** were prepared by conventional coupling between Boc-protected (*S*)-2-aminomethylpyrrolidine (**5d**) and camphorsulfonyl chloride [in situ prepared from camphorsulfonic acid (**6b**) with $SOCl_2$], followed by TFA treatment to produce **3a**. Organocatalyst **3b** was obtained as a single diastereomer after $NaBH_4$ reduction of Boc-protected **3a**, followed by the deprotection of the Boc group. A similar synthetic route was used to prepare **4**: Boc-protected (*S*)-2-aminomethylpyrrolidine (**5d**) was treated with ketopinic acid (**6c**) under standard coupling conditions.[10c]

With pyrrolidinylcamphor compounds **1**–**4** in hand, we explored the catalytic properties of these organocatalysts in the direct α-amination of unmodified aldehydes. Initially, propionaldehyde (**7a**) was chosen as a model substrate and dibenzyl azodicarboxylate (**8a**) was used as the nitrogen source. The reaction was carried out with catalytic quantities of organocatalysts **1**–**4** in toluene at ambient temperature (Table 1). Treatment of **7a** with **8a** in the presence of **1a** (5 mol-%) followed by $NaBH_4$ reduction afforded corresponding primary alcohol **9a** in 96% chemical yield and

Table 1. Direct α-amination of **7a** with **8a** in toluene at ambient temperature by organocatalysts **1**–**4**.[a]



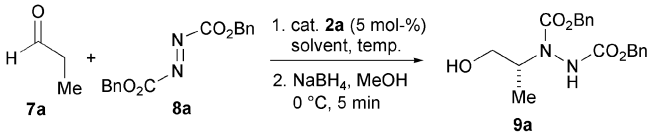
Entry	Catalyst	Time [min]	Yield [%][b]	*ee* [%][c]
1	**1a**	5	96	–16[d]
2	**1b**	5	83	–52[d]
3	**1c**	20	88	31
4	**1d**	5	88	2
5	**1e**	5	91	–39[d]
6	**1f**	5	68	74
7	**2a**	20	90	92
8	**2b**	30	92	90
9	**3a**	90	89	93
10	**3b**	30	78	94
11	**4**	5	80	84

[a] In all cases dibenzyl azodicarboxylate (**8a**; 0.5 mmol) was added to a mixture of propionaldehyde (**7a**; 2.0 mmol) and the appropriate catalyst (5 mol-%). [b] Isolated yield. [c] Determined by chiral HPLC analysis. The newly generated stereogenic center of the major product had the (*R*) configuration. [d] Opposite enantiomer was obtained as the major product.

only 16%*ee* (Table 1, Entry 1). The newly generated stereogenic center of the major product was determined to have the *S* configuration. A slight improvement in the enantioselectivity was obtained when 4-hydroxypyrrolidinyl catalyst **1b** was used (Table 1, Entry 2). Interestingly, the enantioselectivity was reversed when 4-hydroxy-protected silyl ether (OTBDPS) organocatalyst **1c** was used (31%*ee*; Table 1, Entry 3). Unsatisfactory results were achieved when the reaction was performed with organocatalysts **1d**–**f** (Table 1, Entries 4–6). To our delight, catalysts **2a** and **2b** bearing a sulfone linkage provide the desired α-aminated products in high chemical yields and enantioselectivities (92 and 90%*ee*, respectively; Table 1, Entries 7 and 8). Further, sulfonamides **3a** and **3b** and amide **4** organocatalysts also afforded high chemical yields and enantioselectivities (Table 1, Entries 9–11). It is worth noting that the α-aminating reaction required 4.0 equivalents of the aldehyde in the presence of 5 mol-% of the catalyst in a short period of reaction time.

Regarding the reactivity and enantioselectivity, organocatalyst **2a** was chosen for further optimization α-amination studies (Table 2). Changing the solvent to CH_2Cl_2 afforded comparable chemical yields and selectivities as those detected in toluene. However, the catalysis rate was much faster; only 5 min was needed to complete the α-amination process (Table 2, Entry 1). The reactivity and stereoselectivity failed to improve when the reaction was carried out in THF and MeOH (Table 2, Entries 2 and 3). The chemical yields and enantioselectivities were not significantly improved when water and brine were used as the reaction media (Table 2, Entries 4 and 5). Up to 96%*ee* was attained when the reaction was carried out in CH_2Cl_2 at 0 °C, and negligible reaction time was sacrificed (Table 2, Entry 6). Surprisingly, the same level of enantioselectivity was retained when the reaction proceeded with only 2 mol-% of organocatalyst **2a** (Table 2, Entry 7). The reactivity significantly decreased when 0.5 mol-% of organocatalyst **2a** was used under the same reaction conditions (Table 2, Entry 8).

Table 2. Effect of solvent and temperature in the direct α-amination of **7a** with **8a** in the presence of **2a**.[a]

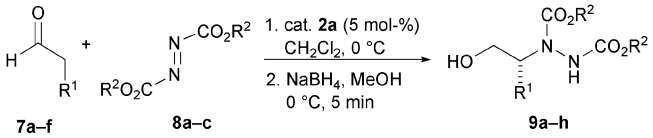


Entry	Solvent	Time [min]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	5	90	92
2	THF	10	84	88
3	MeOH	20	86	86
4	brine	30	86	87
5	H_2O	90	79	87
6[d]	CH_2Cl_2	10	90	96
7[e]	CH_2Cl_2	20	84	95
8[f]	CH_2Cl_2	60	90	95

[a] Unless otherwise specified, in all cases **8a** (0.5 mmol) was added to a mixture of **7a** (2.0 mmol) and **2a**. [b] Isolated yield. [c] Determined by chiral HPLC analysis; major product has the (*R*) configuration. [d] The reaction was carried out at 0 °C. [e] Reaction was carried out at 0 °C with 2.5 mol-% of **2a**. [f] Catalyst **2a** (0.5 mol-%) was added to the reaction mixture at 0 °C.

To assess the general utility of this asymmetric α-amination reaction, we examined the reaction of a variety of alkyl-substituted aldehydes **7a**–**f** with azodicarboxylates **8a**–**c** under optimal reaction conditions (Table 3). Reactions were performed in CH_2Cl_2 at 0 °C in the presence of **2a** (5 mol-%) followed by reduction with $NaBH_4$ at 0 °C. High chemical yields (80–95%) and excellent enantioselectivities (95 to >99%*ee*) were obtained when linear alkyl substrates **7a**–**d** were used (Table 3, Entries 1–4). The reaction with isobutyraldehyde (**7e**) and 3-phenylpropionaldehyde (**7f**) also resulted in satisfactory yields (97 and 93%, respectively) and enantioselectivities (97 and 94%*ee*, respectively; Table 3, Entries 5 and 6). Diethyl and diisopropyl azodicarboxylates (**8b** and **8c**) were also successfully employed in the α-amination process with **7f** under optimal reaction conditions. Aminated alcohols **9g** and **9h** were also obtained in high chemical yields (95 and 97%, respectively) and enantioselectivities (92 and 94%*ee*, respectively; Table 3, Entries 7 and 8).

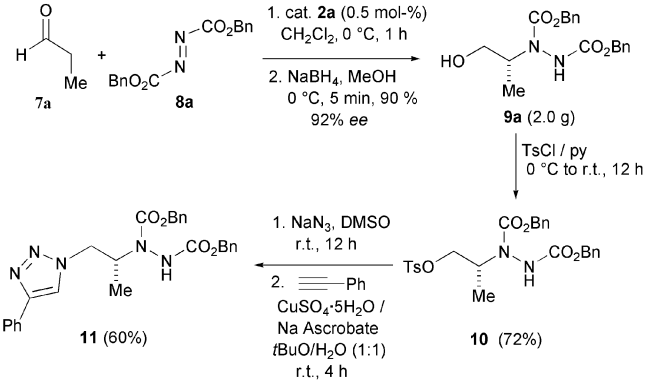
Table 3. Generality of the direct α-amination of various unmodified aldehydes **7a**–**f** with amine sources **8a**–**c** by catalyst **2a**.[a]



Entry	R^1	R^2	Time [min]	Product, Yield [%][b]	*ee* [%][c]
1	Me (**7a**)	Bn (**8a**)	10	**9a**, 90	96
2	Et (**7b**)	Bn (**8a**)	10	**9b**, 95	>99
3	Pr (**7c**)	Bn (**8a**)	10	**9c**, 80	95
4	Bu (**7d**)	Bn (**8a**)	5	**9d**, 91	97
5	*i*Pr (**7e**)	Bn (**8a**)	5	**9e**, 97	97
6	Bn (**7f**)	Bn (**8a**)	10	**9f**, 93	94
7	Bn (**7f**)	Et (**8b**)	5	**9g**, 95	92
8	Bn (**7f**)	*i*Pr (**8c**)	5	**9h**, 97	94

[a] In all cases, azodicarboxylates **8a**–**c** were added to a mixture of aldehydes **7a**–**f** and catalyst **2a** (5 mol-%) in CH_2Cl_2 at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

The utility of this approach is illustrated in the reaction of propionaldehyde (**7a**) with dibenzyl azodicarboxylate (**8a**). The reaction can be easily scaled up to gram quantities (2.0 g) by using organocatalyst **2a** (0.5 mol-%) to give **9a** after $NaBH_4$ reduction, with a 90% isolated yield and high level of enantioselectivity (92%*ee*). As shown in Scheme 2, aminated alcohol **9a** was treated with TsCl in the presence of pyridine, followed by sodium azide treatment and subsequent "click" chemistry[11] under copper-catalyzed cycloaddition to afford enantiomerically enriched triazole derivative **11**. The stereochemistry of the triazole derivative was retained during the reaction process. Triazole derivatives are important building blocks in medicinal chemistry and find various applications in both material science and pharmaceutical research.[12]



Scheme 2. Synthesis of triazole derivative **11** from aminated alcohol **9a**.

Conclusions

In conclusion, we have demonstrated a practical method for the direct α-amination of various unmodified aldehydes with different azodicarboxylates catalyzed by structurally rigid pyrrolidinylcamphor organocatalysts **1**–**4**. The desired α-aminated alcohols were obtained with high to excellent chemical yields and excellent enantioselectivities (up to >99%*ee*) when the reaction was performed with catalyst **2a** (5 mol-%) in CH_2Cl_2 at 0 °C. These data compare favorably to the best results reported previously, and this method represents an alternative, efficient α-amination of unmodified aldehydes. More studies are underway.

Experimental Section

General Procedure for the Asymmetric α-Amination: To a stirred solution of catalyst **2a** (0.025 mmol) and aldehyde **7a**–**f** (2.0 mmol) in CH_2Cl_2 (0.5 mL) cooled to 0 °C was added azodicarboxylate **8a**–**c** (0.5 mmol) at the same temperature. The reaction mixture was stirred at 0 °C for the time indicated in Tables 2 and 3. After the azodicarboxylate was consumed as indicated by TLC analysis (the decolorization of azodicarboxylate was also observed), the reaction was treated with sodium borohydride (0.5 mmol, 20 mg) in methanol (0.5 mL). After 5 min, the reaction was quenched with aqueous NH_4Cl (1 mL) and brine. The mixture was extracted with ethyl acetate (2 × 20 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 1:8 to 1:4) to afford pure α-aminated products **9a**–**h**.

Supporting Information (see footnote on the first page of this article): Representative experimental procedures for organocatalysts **1**–**3**, **9a**, **10**, and **11** with all spectroscopic data; HPLC chromatograms for **9a**–**h**.

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