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Direct Synthesis of Polyamides via Catalytic Dehydrogenation of Diols and Diamines

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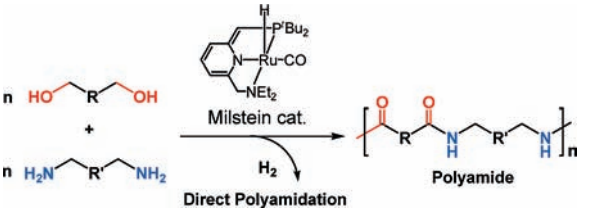
Supporting Information

ABSTRACT: We report a direct synthesis of polyamides via catalytic dehydrogenation of diols and diamines. A PNN pincer ruthenium complex, the Milstein catalyst, was used for this reaction and polyamides with number average molecular weight from ~10 to 30 kDa could be obtained from a wide variety of diols and diamines bearing aliphatic or aromatic, linear or cyclic spacers. Because of the high catalytic selectivity of primary amine over secondary amine, polyamines could be conveniently incorporated into linear polyamides without tedious protection/deprotection steps. Compared with conventional condensation method, this catalytic system avoids the requirement of stoichiometric preactivation or *in situ* activation reagents and provides a much cleaner process with high atomic economy.

Natural and synthetic polyamides are among the most important families of polymers. Natural polyamides, including proteins and peptides, are essential macromolecules in living organisms. Synthetic polyamides exhibit high strength, toughness, and stability, and therefore have received numerous applications in fiber products and engineering plastics,[1] and recently found great potentials for many functional applications.[2] In biomedical studies, polyamides have also attracted much attention because they have shown good biocompatibility and degradability.[3] For example, polylysine (PLL) and poly(amido amine) dendrimer (PAMAM) as well as their derivatives have been widely used in biomaterial applications.[4,5] Our lab has previously developed functional polyamides as biomaterials for gene delivery,[6] tissue engineering,[7] and protein-resistant applications.[8] The growing interest in polyamide-based functional materials and biomaterials has motivated us to develop more efficient direct synthesis of functional polyamides.

Polyamides are conventionally synthesized by condensation between amines and carboxylic acids or their derivatives. In such reactions, the acids are usually preactivated to form acyl chlorides[2] or active esters,[9] or *in situ* activated by stoichiometric amounts of coupling reagents,[10] the latter being used extensively in peptide synthesis.[11] High temperature melt condensation is used for commercial synthesis of aliphatic polyamides (Nylons).[1] All these syntheses involve harsh conditions and/or produce stoichiometric amount of toxic wastes. Alternatively, polyamides can also be produced by ring-opening polymerizations of lactams[12] or *N*-carboxyamino acid anhydride.[13] However, the preparation of the cyclic monomers still encounters the same limitations aforementioned for amidation reaction. While several mild amidation methods have been developed for peptide synthesis,[14,15] their efficiency and substrate scope have hindered their application for polyamide synthesis. Given the broad importance of polyamides for both technological and biomedical applications, an atom economic synthesis that avoids toxic waste generation and/or harsh conditions is highly desirable.

Scheme 1. Concept of Direct Polyamidation via Dehydrogenation



Milstein and co-workers recently reported a direct dehydrogenative amidation from alcohols and amines using a PNN pincer Ru catalyst.[16] Following this seminal work, several other groups reported similar amidation systems, which feature Ru catalysts with bidentate ligands[17] and NHC ligands,[18−20] rhodium catalysts[21] and supported silver catalysts.[22] Given the high efficiency of the catalytic process and minimal side product (H_2) generated, we were inspired to apply this catalytic reaction to polyamide synthesis (Scheme 1). Herein, we report the first successful direct polyamidation from diols and diamines using the Milstein Ru catalyst.

In Milstein's original paper, while both mono- and diamines were shown suitable for the catalytic amidation, only the reactions of monoalcohols have been reported.[16] Therefore, we first investigated the reactivity of diols by running model reactions between a series of alkyl diols and benzylamine (Scheme S1 in the Supporting Information). Surprisingly, the results show that a minimum spacer of six carbons between the two hydroxyl groups is necessary for an efficient conversion. The exact reason for the inactivity of diols with shorter spacers is unclear at this moment, which could be due to chelation of the two hydroxyl groups to the active catalytic center. It is worth noting that this effect is only for free hydroxyl groups, because oxygen atoms in oligo(ethylene glycol)s used in later studies do not affect the catalytic activity.

Next, a model polyamidation between tri(ethylene glycol) (**1a**) and *m*-xylylene diamine (**2a**) was chosen to optimize polymerization conditions (Table 1). Oligo(ethylene glycol)s (OEGs) were

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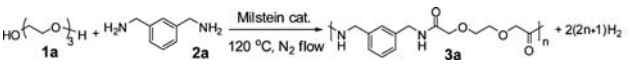
Table 1. Condition Screening for a Model Catalytic Polyamidation[a]



entry	cat. loading (mol %)	reaction time (h)	solvent	converion (%)[b]	M_n (10^3)[c]	PDI[d]
1	0.2	28	toluene	56	<1.0[e]	-
2	0.5	28	toluene	77	1.1	1.14
3	0.5	48	toluene	82	1.6	1.92
4	1.0	48	toluene	89	3.2	1.59
5	1.0	48	anisole	>99	13.8	1.67
6	1.0	48	DMSO	79	1.4	1.60
7	1.0	48	anisole/DMSO (6:1)	>99	22.6	1.51

[a] Reaction condition: 1.0 mmol triglycol, 1.0 mmol xylylenediamine, and 0.01 mmol catalyst are premixed in 1.5 mL solvent in glovebox, then heated under N_2 flow. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Number average molecular weight, determined by Gel Permeation chromatography (GPC). [d] Polydispersity index, determined by GPC. [e] No polymer peak in GPC, only oligomers observed by ^{1}H NMR.

chosen in our model study because they offer sufficient distance between the two −OH groups, have good solubility, and they are FDA approved biomaterials having minimal cytotoxicity and immunogenicity.[23] Initially, we followed the same conditions reported in Milstein's original paper for dehydrogenation. Heating a mixture of **1a** and **2a** with 0.2 mol % Milstein catalyst for 28 h, however, only resulted in mostly dimers and trimers (entry 1). Increasing catalyst loading and reaction time has moderate positive effect on the polymerization (entries 2−4); but the molecular weight of the polymer was still relatively low (number-averaged molecular weight, M_n < 3 kDa). One possible factor is that, due to extensive hydrogen bonding between amide linkages, the resulting polyamide has limited solubility in toluene, which may prematurely stop chain growth. To address this issue, we reasoned that more polar solvents should break the interchain hydrogen bonds and increase the solubility. Therefore, several polar solvents were screened (Table S1 in the Supporting Information) and anisole was found to be a good solvent in which the catalyst remained highly active and the M_n of the polyamide was dramatically increased (entry 5). Too polar solvents such as DMSO seemed to suppress the activity of the dehydrogenation reaction (entry 6); however, addition of a relatively small amount of DMSO to anisole could increase the polarity without significantly lowering catalyst activity, and thus, the M_n of the polymer could be further improved to more than 22 kDa (entry 7). For even less soluble polymers, the ratio of DMSO could be further increased to obtain better polymerization results (Table 2, entries 1−3).

Employing our optimized condition, we then synthesized a series of polyamides using various diols and various diamines (Table 2). Because the ultimate molecular weight of each polymer is greatly affected by its solubility in the polymerization solution, either anisole or anisole/DMSO mixed solvent was used for optimal result. We observed that, while anisole/DMSO mixed solvent worked better for less soluble polyamides (entries 1−3), anisole gave larger polymers for more soluble systems (entries 4−17), because the addition of DMSO increased the polyamide solubility while decreased the catalyst activity. With oligo(ethylene glycol)s as diol monomers, a variety of diamines, having aliphatic or aromatic, linear or cyclic spacers, were effective for the polyamidation, resulting in polymers with M_n ranging from 10 to 30 kDa (entries 1−7). For diamines having longer alkyl chain between two amino groups, the polymer become less polar and more soluble in anisole; therefore, dodecanediamine (**2e**) gives much larger polymer than propanediamine (**2d**). Trifunctional monomer, tris(2-aminoethyl)amine (**2h**), could also be incorporated into the polyamide, resulting in a branched polymer (entry 8). ^{1}H NMR data confirms the incorporation of the triamine into the polymer, indicating a branching structure (see Supporting Information).

To further test the scope of the method, various diols with linear or cyclic, aliphatic or aromatic spacers were shown to be suitable for polymerization with diamine under the same conditions (entries 9−13). Because of low solubility, polymerization of simple alkane diols precipitated prematurely. However, copolymerization of an alkane diol with tetra(ethylene) glycol (1:1) afforded polyamides with molecular weight higher than 20 kDa (entries 12−13) because the resulting polymers have much better solubility. On the basis of the composition of the copolymers revealed by ^{1}H NMR data (see Supporting Information), the two diols have almost identical reactivity for polymerization. It should be noted that, due to limited solubility and phase separation during polymerization, some systems gave bimodal molecular weight distribution in GPC measurement .

The dehydrogenative polyamidation should follow a similar catalytic process as proposed by Milstein et al.[16] Presumably, after a catalytic cycle for dehydrogenation of an alcohol to the corresponding aldehyde, reaction with an amine will form the hemiaminal, which is subsequently converted to an amide linkage by a second catalytic cycle of dehydrogenation. One interesting feature of the Milstein catalyst is the selectivity for primary amines in presence of an unprotected secondary amine.[16] This offers an exciting opportunity for direct synthesis of functional polyamides containing secondary amino groups circumventing tedious protection and deprotection steps.[24] To test this selectivity in polyamidation, diethylene triamine (**2i**), and naturally occurring spermidine (**2j**) and spermine (**2k**) were directly used in the polyamidation without any protection (entries 14−16). On the basis of ^{1}H NMR analysis, the secondary amines in polymers **3o**−**3q** remain intact during the direct polyamidation (Figures S1−S5 in the Supporting Information). With natural polyamines and biocompatible OEGs, these cationic polymers are promising candidates for biomedical, such as gene delivery, applications. In the same manner, piperazinediethanol (**1e**) could also

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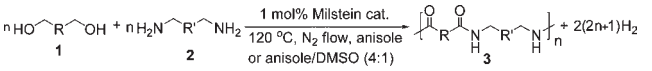
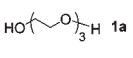
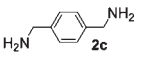
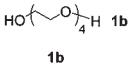
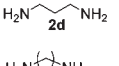
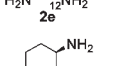
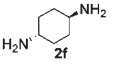
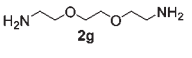
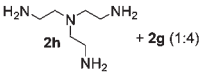
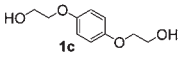
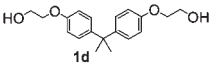
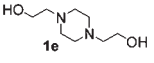
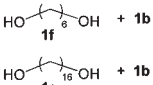
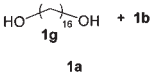
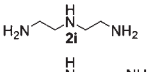
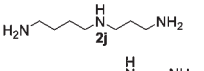
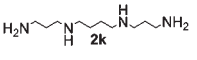
Table 2. Catalytic Dehydrogenative Polyamidation[a]



Entry	Diol	Diamine	Conversion[b] (yield[c]) (%)	M_n (10^3)	PDI
1[d]	 1a	 2c	99 (89) 3b	11.9	3.09
2[d]	 1b	2c	>99 (87) 3c	12.7	2.80
3[d]	1b	 2d	>99 (84) 3d	19.8	1.86
4[e]	1b	 2e	>99 (88) 3e	28.4	1.75
5[e]	1b	 2f	98 (77) 3f	13.6[f]	-
6[e]	1a	 2g	>99 (73) 3g	19.4	1.59
7[e]	1b	2g	>99 (78) 3h	22.1	1.56
8[e]	1b	 2h + 2g (1:4)	>99 (71) 3i	21.2[g]	2.12
9[e]	 1c	2g	99 (85) 3j	15.0	1.59
10[e]	 1d	2g	>99 (79) 3k	16.5	1.69
11[e]	 1e	2g	>99 (76) 3l	19.5	1.65
12[e,i]	 + 1b (1:1)	2g	>99 (88) 3m	24.2	1.65
13[e,i]	 + 1b (1:1)	2g	>99 (90) 3n	21.5	1.63
14[e,i]	1a	 2i	99 (91) 3o	8.2	2.89
15[e]	1b	 2j	97 (65) 3p	6.8[h]	2.56
16[e]	1b	 2k	99 (70) 3q	9.6[h]	1.65
17[e]	1e	2i	99 (72) 3r	11.3[h]	3.06

[a] Reaction conditions: 1.0 mmol diol, 1.0 mmol diamine and the Ru catalyst are premixed in 1.5 mL solvent in glovebox, then heated under N_2 flow for 48 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Isolation yield after precipitation in toluene. [d] In anisole/DMSO (4:1), 2 mol % catalyst loading. [e] In anisole, 1 mol % catalyst loading. [f] Not soluble in GPC solvent, calculated from ^{1}H NMR. [g] Molecular weight measured by Multi-Angle Laser Light Scattering (MALLS). [h] GPC taken after acylation by Ac_2O to avoid strong interaction with the GPC column gel material. [i] Reaction carried out at 2.5 mmol scale.

polymerize with polyamines, giving a linear polyamide with even higher cationic charge density on polymer backbone (entry 17).

In conclusion, we report here the first successful direct polyamidation by catalytic dehydrogenation of diols and diamines. The polymerization is applicable to a wide variety of diols and diamines containing linear or cyclic, aliphatic or aromatic, spacers. This method avoids the stoichiometric preactivation or *in situ* activation reagents required for conventional polyamidation method and provides a much cleaner process with high atomic economy. The high catalytic selectivity of this method also offers the opportunity of efficient synthesis of functional polyamides. Given the broad importance of functional polyamides, this atom economic polyamidation may find widespread utility in many technological and biomedical applications. Our current focus is on investigation of different dehydrogenation catalytic systems for further broadening the scope of this method as well as on application of this method to the synthesis of highly functional polyamides as new biomaterials.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, synthesis, characterization data, and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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