Organic & Biomolecular Chemistry

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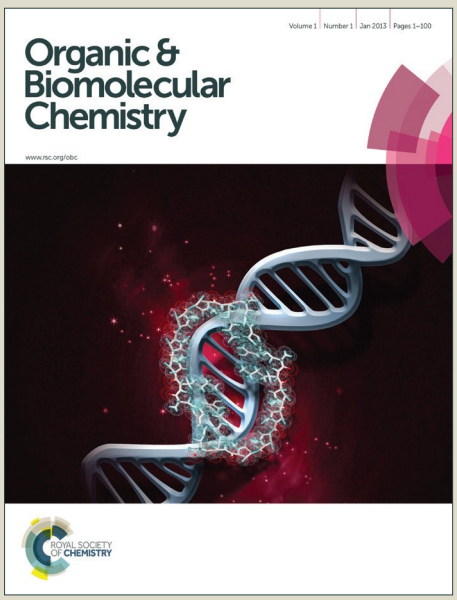

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PAPER

Base-mediated self-propagative Lossen rearrangement of hydroxamic acids for the efficient and facile synthesis of aromatic and aliphatic primary amines

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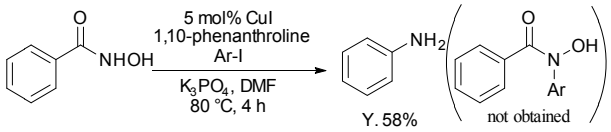
A variety of aromatic and aliphatic hydroxamic acids were converted to the corresponding primary amines *via* base-mediated rearrangement. This rearrangement could proceed in less than 1 equiv. of K_2CO_3 in polar solvents under thermal condition with no external reagents. This rearrangement has several features including no external activating agents to be needed for promoting the rearrangement, a less than one equivalent of base to be used, and a clean reaction in which only carbon dioxide is produced as a by-product. A self-propagating mechanism *via* an isocyanate intermediate is proposed and elementary reaction steps, namely, chain propagation reactions are supported by experiments.

Introduction

Primary amines are fundamentally important compounds and are extensively utilized in organic synthesis. As a result, the development of new experimental methods that enable easier access to them in a one-pot procedure with less waste production is of great concern. The Hofmann, Curtius, Schmidt, and Lossen rearrangements are well known as general methods for the synthesis of amines from carboxylic acid derivatives with a loss of carbon dioxide.[1] In the Lossen rearrangement, *O*-acylation of hydroxamic acids is a necessary step before the rearrangement,[2] and this preliminary process makes synthetic application of the Lossen rearrangement less attractive than the related above reactions, although the Lossen rearrangement can be carried out in relatively mild reaction conditions, enabling the large scale synthesis of primary amines.[3] Therefore, a variety of modifications of the Lossen rearrangement have been reported in the past 60 years. The most common activation methods to promote the Lossen rearrangement are *in situ* activation of free hydroxamic acids using a stoichiometric amount of activating agents such as dimethyl carbonate,[4] 4-NBsOXY,[5] carbonyldiimidazole,[6] cyanuric chloride,[7] azodicarboxylate and triphenylphosphine (Mitsunobu condition),[8] *N,N'*-dicyclohexylcarbodiimide,[9] polyphosphoric acid,[10] bromodimethylsulfonium bromide,[11] *N*-methylimidazole[12], sulfonyl chlorides[13] *etc.* However, in most cases, obtained products were not amines but ureas or carbamates, which were often difficult to be further transformed into other functionality including free amino group, thus leading to reduce synthetic value of the reaction in organic synthesis. Some carbamates are also well known to be smoothly transformed into primary amines, but it requires multi steps.

Recently we encountered an unexpected result that aniline was exclusively obtained instead of *N*-arylhydroxamic acid when examining *N*-arylation of benzhydroxamic acid with aryl iodide catalyzed by copper catalyst, which means occurrence of C to N migration of the aryl group[14] (Scheme 1). After our preliminary examination, we found that this rearrangement has an outstanding feature that without using external activating agent free aromatic hydroxamic acids (*N*-unsubstituted hydroxamic acids, also named primary hydroxamic acids) can be selectively converted to anilines.



Scheme 1 A trial of N-arylation of hydroxamic acid.

To date, few examples were reported on Lossen rearrangement of free hydroxamic acids in the absence of external activating agents. Two research groups reported the production of *N,N'*-diphenylurea instead of aniline through Lossen reaction. Spontaneous Lossen rearrangement of *in situ* generated (phosphonoformyl)hydroxamates to phosphoramidates was also reported.[15] As a notable exception Kobayashi *et al.* reported a small production of perfluoroaniline as a by-product in the treatment of electron-

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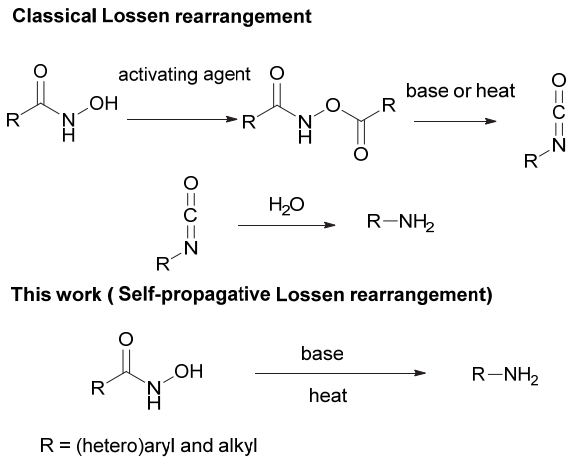
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

deficient perfluorobenzohydroxamic acid with K_2CO_3 in boiling water.[16] On the other hand, Roithova *et al.* reported metal-assisted Lossen rearrangement of free hydroxamic acids, and they suggested that Lossen rearrangement would proceed by free hydroxamic acids activated by potassium ion.[17] Recently, S. B. King et al. reported that Lossen rearrangement can be proceeded under Heck reaction conditions ($Pd(OAc)_2$ and Et_3N).[18] In this reaction, aromatic hydroxamates were converted to anilines, ureas, and carbamates, but aliphatic compounds afforded only ureas. Unfortunately, these methods described above relating to Lossen rearrangement without external activating agents are insufficiently investigated for the scope and limitations of substrates and were difficult to selectively obtain primary amines. Herein we wish to report the self-propagative Lossen rearrangement of a variety of aromatic and aliphatic hydroxamic acids to primary amines without external activating agents. To explain this reaction, a plausible reaction mechanism was proposed and some experiments supporting it were carried out. Because of advantage associated with no use of additional reagent for activation, the direct synthesis of not only anilines but also aliphatic primary amines from free hydroxamic acids is more attractive (Scheme 2).

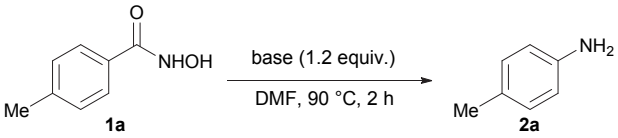


Scheme 2 Self-propagative Lossen rearrangement of free hydroxamic acids.

Result & Discussion

Initial attempts to optimize the reaction conditions for rearrangement of hydroxamic acids to the corresponding amines were performed with *p*-methylbenzohydroxamic acid as starting material in the presence of inorganic or organic bases in DMF (Table 1). The desired product, *p*-toluidine, was obtained in low yields when Li_2CO_3 was used (entry 1). The use of K_2CO_3, Cs_2CO_3, K_3PO_4, and DBU provided better yields of the aniline (Table 1, entries 3-5, 12). Notably, the reaction proceeded even in the presence of an organic base like DBU, whose result is inconsistent with Roithova's hypothesis[17] that metals might activate hydroxamic acids to induce the rearrangement. We found that the yields of toluidine in the series of experiments were related to the values of p*K*a of conjugated acids. These results indicate that p*K*a values of conjugate acids of bases are likely required to be more than 9 in order to effectively promote the reaction, which the value is near equal to that of hydroxamic acids. Indeed, rearrangement did not proceed when K_2HPO_4, Imidazole, Et_3N, and DIPEA were used. The use of Ag_2O induced the rearrangement, but the aniline produced was further oxidized by Ag_2O to give *p*-nitrotoluene. In the absence of base, the reaction did not proceed at all and the starting compound hydroxamic acid was recovered in 90% yield (entry 12). Although the use of Cs_2CO_3, K_3PO_4, and DBU gave similar yields of the product compared to K_2CO_3, the latter was chosen for further study since it is much cheaper than them.

Table1 Effect of inorganic or organic bases in self-propagative Lossen rearrangement



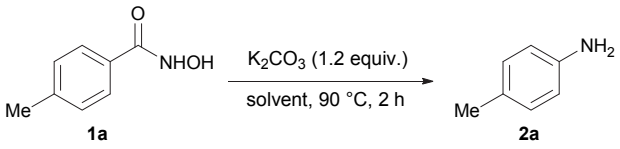
1a **2a**

entry	base	yield (%)
1	Li_2CO_3	12
2	Na_2CO_3	81
3	K_2CO_3	92
4	$CsCO_3$	93
5	K_3PO_4	96
6	K_2HPO_4	trace
7	Ag_2O	-
8	imidazole	trace
9	Et_3N	trace
10	DIPEA	trace
11	DBU	97
12	none	-

Next, various solvents were examined (Table 2). The values of dielectric constant ε and π^*, known as a scale of solvent dipolarity/polarizability,[19] are also shown together in Table 2. High-polar aprotic solvents such as DMSO, DMF, and NMP provided the aniline in good yields (Table 2, entries 1-3). Propylenecarbonate and propionitrile were also examined to give *p*-toluidine in moderate yields (Table 2, entries 4,5). *p*-Toluidine was obtained in low yield when 2-methoxyethanol was used (Table 2, entry 6). These results suggest that the presence of proton source inhibits the rearrangement partly due to the deactivation of intermediates (*vide infra*). When 1,2-dichloroethane (DCE) was examined, the reaction scarcely proceeded because of lower solubility of the hydroxamic acid. In addition, *p*-toluidine was not obtained, but *N*-(2-chloroethyl)aniline was isolated in low yield, which is probably produced by further reaction of aniline with DCE. Lower boiling solvents (MeOH, THF, and diisopropylether) were examined at reflux condition, but it resulted in low yields. It is noteworthy that, as shown above, increasing the polarity of solvents leads to significantly improve the yields of the aniline. It is apparent that this reaction is substantially influenced by the polarity of solvents. It was found that the yield data show much more

correlation with the π* values than with the dielectric constants ε. Although the reason for this is not clear, it seems reasonable to suppose that the ability to stabilize a charge or dipole of reaction intermediates and/or transition-state species in reaction affects the product yields since π* scale is related to the solvent's ability to do that. Lowering the reaction temperature (70 °C) could also afford the aniline in a good yield but it needed much longer reaction time. It should be noteworthy that the rearrangement could proceed even though using less than 1 equiv. of K_2CO_3. Indeed, 0.5, 0.05, and 0.01 equivalents of K_2CO_3 provided the aniline in 97%, 91%, and 65% yields, respectively, although it was needed much longer reaction time until the reaction completely finished when below the 0.05 equivalents is used. Finally, we investigated the effect of H_2O. The reaction was performed along with 0.5 equiv. of K_2CO_3 and 3 vol% H_2O under air, giving the product in lower yield (63%). This result implied that hydrolysis of isocyanate intermediate would inhibit this reaction (*vide infra*).

Table 2 Effect of solvents in self-propagative Lossen rearrangement



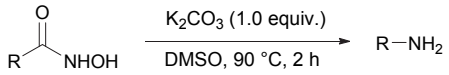
1a **2a**

entry	solvent	ε^b	π^{*c}	yield (%)
1	DMSO	46.71	1.00	98
2	DMF	37.06	0.88	92
3	NMP	32.58	0.92	90
4	propylenecabonate	62.93	0.83	68
5	propionitrile	28.86	0.64	68
6	2MeOEtOH	16.93	0.71	39
7	MeCN[a]	36.00	0.66	21
8	MeOH[a]	32.35	0.60	10
9	toluene	2.43	0.49	12
10	*n*-BuOH	17.51	0.47	11
11	*t*-BuOH	12.47	0.41	8
12	DCE	10.74	0.73	-
13	THF[a]	7.47	0.55	-
14	diisopropylether	4.04	0.19	-

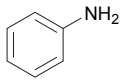
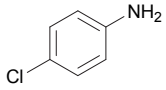
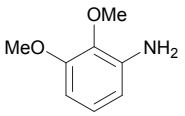
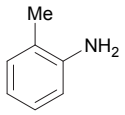
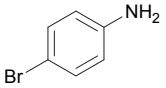
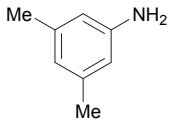
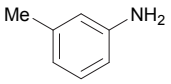
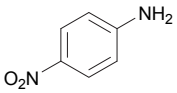
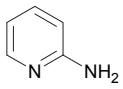
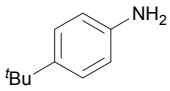
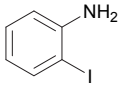
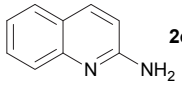
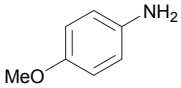
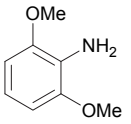
[a] The reaction were heated at reflux. [b] ε is dielectron constant of the solvents. [c] π* is polarity of the solvents.

With the optimized conditions in hand, the scope of aromatic hydroxamic acids were examined (Table 3). In the presence of 1.0 equiv. of K_2CO_3 in DMSO at 90 °C, the parent compound benzohydroxamic acid was transformed into aniline in excellent yield (Table 3, entry 1). Next, substituted aromatic hydroxamic acids were subjected to the reaction conditions (entries 2-12). When the electron-donating group (*e.g. o*-, *m*-, *p*-methyl and *p*-MeO) substituted substrates were employed, the corresponding products were obtained in high yields (Table 3, entries 2-5). The benzohydroxamic acids having electron-withdrawing group at ortho- or para-position were also good substrates to give the desired anilines in high to excellent yields (Table 3, entries 6-9). The reaction of *p*-nitrobenzohydroxamic acid (**1j**) gave the corresponding aniline in good yield, but it needed much longer reaction time. It is noted that when the substrates having electron-withdrawing group were subjected to the reaction conditions (Table 3, entries 7-8, 10), the yields of the products were slightly decreased and a small amount of the corresponding carboxylic acids were obtained as by-products in low yields (*p*-Cl (9%), *p*-Br (7%), and *p*-NO_2 (10%)). The *o*-substituted substrates were converted into the corresponding anilines in high yields despite steric hindrance of the substituents (entries **2c**,**j**,**k**, and **l**). Additionally, in the case of electron-rich 2,6-dimethoxybenzhydroxamic acid, an intense foam generation occurred at around 90 °C and the rearrangement was completed within 5 min. This result is consistent with ortho effect of Lossen rearrangement, in which the existence of *o*-substituent, even electron-withdrawing group, accelerates the rate of migration.[20] Next we examined heterocyclic compounds (Table 2, entries 13-14). The desired hetarylamines 2-aminopyridine (**2n**) and 2-aminoquinoline (**2o**) were obtained in good yields. In the all cases any regioisomer of each product was not detected at all. This high regioselectivity appeared to be a great merit compared to the conventional methods for preparing the amines through electrophilic aromatic substitution with nitrogen electrophile, which frequently suffer from the regioselectivity of the reaction. In addition, the present rearrangement can give haloanilines in good to excellent yields with higher chemoselectivity than reduction of halogenated aromatic nitro compounds, which has a problem with the chemoselectively.

Table 3 Substrate scope of aromatic hydroxamic acids



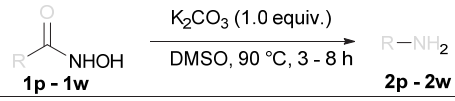
1a - 1o **2a - 2o**

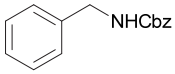
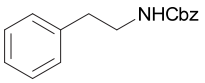
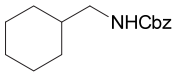
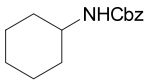
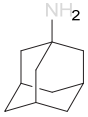
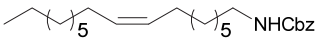
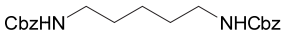
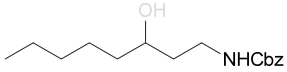
Entry	Product		Yield (%)	Entry	Product		Yield (%)	Entry	Product		Yield (%)
1		**2b**	96	6		**2g**	90	11		**2l**	99
2		**2c**	99	7		**2h**	92	12		**2m**	97[c]
3		**2d**	99	8		**2i**	88[a]	13		**2n**	74[d]
4		**2e**	90[c]	9		**2j**	96	14		**2o**	74
5		**2f**	99	10		**2k**	98[b]				

[a] The reaction was performed for 9 hours in 4 ml of DMSO in order to solve the reaction mixture. [b] The reaction time is 5 min. [c] The reaction time is 4 hours. [d] The reaction time is 12 hours.

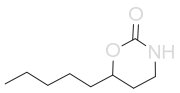
Next, various aliphatic compounds were examined for the present rearrangement. In most cases, amine products were isolated as Cbz-protected forms in order to simplify the isolation of aliphatic primary amines. *prim*-Alkyl amines were obtained in good yields, but it needed longer reaction time and a small amount of urea was observed as a byproduct (Table 4, entries 2 and 3). α-Branched aliphatic hydroxamic acid **1q** was also transformed into the desired amine **2q** in high yield (Table 4, entry 4). When sterically hindered hydroxamic acid **1r** was employed, the corresponding amine **2r** could be obtained in high yield without Cbz protection (Table 4, entry 5). The unsaturated aliphatic hydroxamic acid **1s** was subjected to the rearrangement to give the corresponding amine in high yield (Table 4, entry 6). Aliphatic dihydroxamic acid **1t** did not afford diamine but urea as a by-product (Table 4, entry 7). In the case of hydroxamic acid having hydroxy group, rearrangement and subsequent intermolecular cyclization occurred to give oxazoline **2w'** in 29% yield instead of amine (entry 8). It is probably a result of the intramolecular trap of isocyanate intermediate by hydroxy group at 3 position.

Table 4 Substrate scope of aliphatic hydroxamic acids



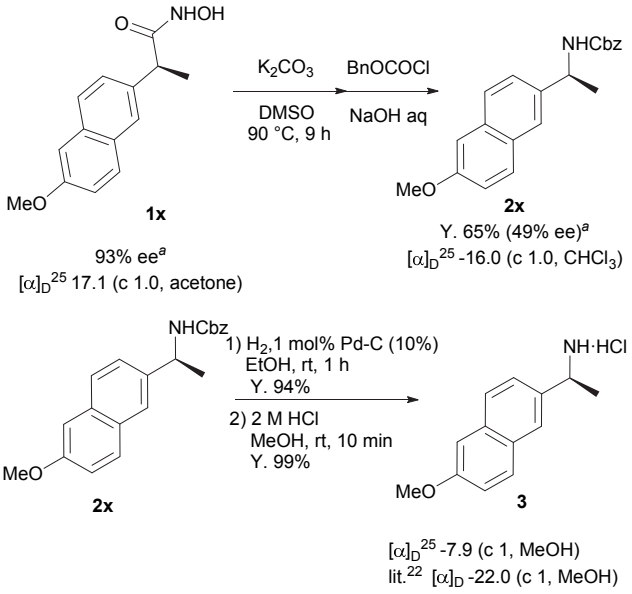
Entry	Product		Time (h)	Yield (%)
1		**2p**	3	95
2		**2q**	6	82
3		**2r**	8	80
4		**2s**	6	98
5		**2t**	3	98
6		**2u**	7	95
7		**2v**	4	-
8		**2w**	28	-[a]

a



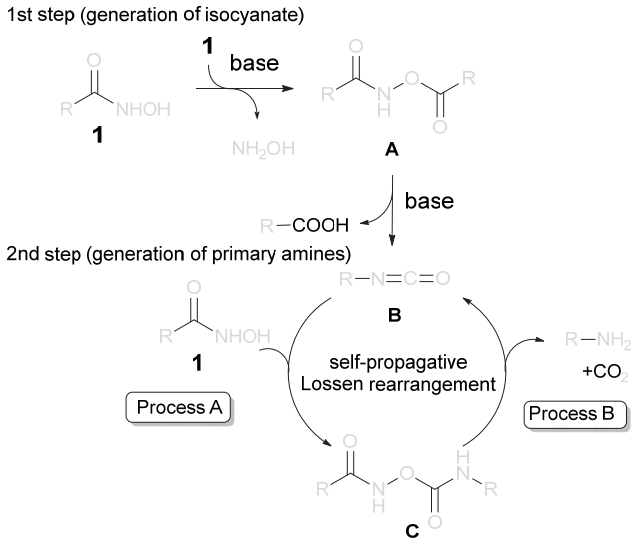
2w' (29% yield)

To further explore the usefulness of the present rearrangement, we next focused on the reaction of optically active hydroxamic acid (Scheme 3). Previous studies showed that the Lossen rearrangement proceeded in a stereospecific manner with retention of configuration of the migrating group.[21] Optically active naproxen amine (1-(6-methoxynaphth-2-yl)ethylamine) has stronger fluorescence and examined as a chiral derivatizing agent for the liquid chromatographic fluorescence assay of chiral carboxylic acids.[22] (*S*)-Naproxen hydroxamic acid was synthesized from (*S*)-Naproxen via the reaction of ester with hydroxylamine and the optically purity was checked by comparison of the specific rotation and chiral HPLC (93% ee).[23] (*S*)-Naproxen hydroxamic acid prepared was subjected to the present rearrangement conditions to give the desired Cbz-protected amine in a good yield, but the reduction of optical purity was observed (49% ee). It was further transformed to amine hydrogen chloride in order to confirm the optical purity. The low value of the specific rotation was observed compared to the literature one.[22]



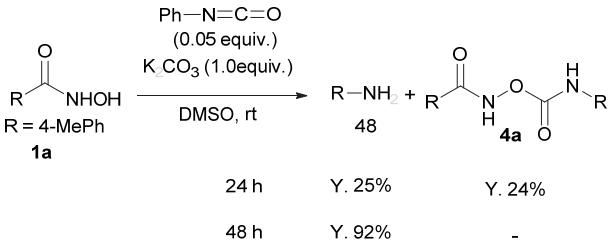
Scheme 3 Synthesis of optically active naproxen amine. [a] Determined by chiral HPLC

A plausible reaction mechanism for the present rearrangement is shown in Scheme 4. First, two molecules of hydroxamic acids would react each other in the presence of base to give an *O*-acyl hydroxamate A (1st step), the subsequent rearrangement of which would arise to give an isocyanate B along with released of an equimolar amount of carboxylate. Then generated isocyanate should react with hydroxamic acid under basic conditions (Process A in 2nd step) to give a *O*-carbamoylhydroxamate C, and isocyanate might be reproduced via rearrangement (Process B in 2nd step). Meanwhile, an amine is generated along with decarbonation. Finally, reproduced isocyanate induces the same process, leading to repeat these reactions. As mentioned above, *p*-electron-withdrawing substituted aromatic hydroxamic acids afforded a small amount of carboxylic acids along with the desired anilines. It is considered that the rate of rearrangement of *O*-carbamoylhydroxamate C in 2nd step would be slower than that of electro-donating substrates and therefore 1st step reaction maybe proceed substantially compared with 2nd step, leading to produce the carboxylic acids as py-products.



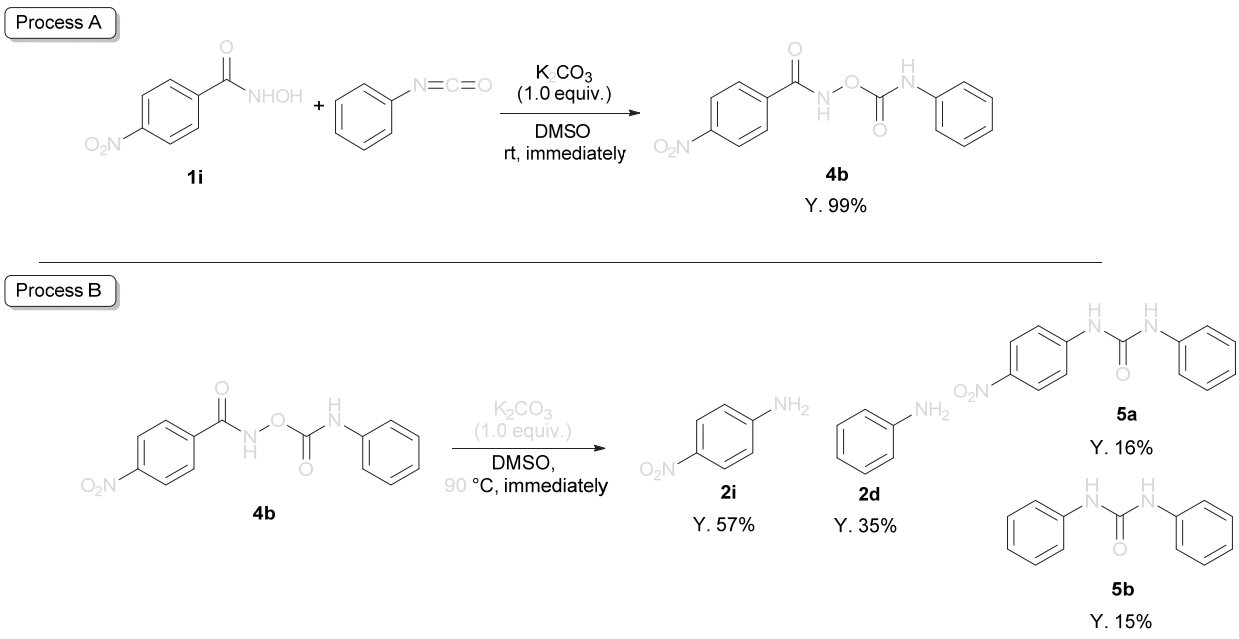
Scheme 4 A plausible mechanism of self-propagative Lossen rearrangement

Based on this working hypothesis, the generation step of *O*-acyl hydroxamate A would be a rate-determining step. Therefore, in order to obtain a clue that isocyanate is *in situ* generated from two equivalents of hydroxamic acids, *p*-methylbenzohydroxamic acid was reacted with K_2CO_3 in the presence of a catalytic amount of phenylisocyanate in DMSO under room temperature (Scheme 5).[24] After stirring for 24 h, 4-methylaniline **2a** was obtained in 25% yield, while *O*-carbamoyl hydroxamate **4a** was obtained in 24% yield, indicating that hydroxamic acid was reacted with *in situ* generated isocyanate. On the other hand, for 48 h stirring 4-methylaniline **2a** was obtained in high yield and *O*-carbamoyl hydroxamate **4a** was not obtained. It is suggested that aniline was generated via rearrangement of *O*-carbamoyl hydroxamate **4a**, and implying that the isocyanate intermediate would be reproducibly generated in that reaction.



Scheme 5 Reaction of *p*-methylbenzohydroxamic acid with K_2CO_3 and a catalytic amount of phenyl isocyanate in DMSO at room temperature.

Next, we investigated *O*-acylation of hydroxamic acid with isocyanate (Scheme 6). The reaction of 4-nitrobenzhydroxamic acid with phenyl isocyanate was conducted in the presence of 1.0 equiv. of K_2CO_3 in DMSO at room temperature to check the Process A in 2nd step. *O*-Acylation of hydroxamic acid smoothly proceeded to give *O*-carbamoylhydroxamate **4b** in an excellent yield.[25] Subsequently, to confirm the Process B, *O*-carbamoylhydroxamate was heated in the presence of K_2CO_3 to give 4-nitroaniline (**2i**) as a major product. In addition, unsymmetrical urea **5a** and symmetrical **5b** were also obtained. It is suggested that isocyanate was generated from *O*-carbamoylhydroxamate **4b,** and some isocyanates reacted with anilines **2i** and **2d** due to the absence of hydroxamic acid.



Scheme 6 *o*-Acylation of hydroxamic acid with isocyanate and rearrangement of *O*-carbamoylhydroxamate in the presence of K_2CO

Based on the above experimental results and discussion, we may conclude that: in 1st step, isocyanate is generated via rearrangement of *O*-acyl hdroxamate formed by two molecules of hydroxamic acids reacted in the presence of base, and in 2nd step, generated isocyanate and hydroxamic acid were reacted to give *O*-carbamoyl hydroxamate, followed by rearrangement is leading to isocyanate B. As a result, isocyanate is obtained again and primary amine is produced along with decarbonation. It is likely that the rate of 2nd step would be faster than that of 1st step, consequently 2nd step is repeated many times, and then hydroxamic acid is converted into primary amine. In other words, this reaction might proceed by a chain reaction. Therefore we would like to call this reaction self-propagative Lossen rearrangement.

Conclusions

In conclusion, we investigated self-propagative Lossen rearrangement of various aromatic or aliphatic hydroxamic acids to primary amines without using activating agent. This rearrangement took place in the presence of inorganic or organic base under thermal condition in polar aprotic solvents. A self-propagating mechanism *via* isocyanate intermediate is proposed and elementary reaction steps, namely, chain propagation reactions are supported by experiments. This method is promising as a facile synthesis of amines and a clean reaction in which only carbon dioxide is produced as a by-product.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR PARAGON 1000 spectrometer or a JASCO FT/IR-4100. ^{1}H NMR spectra were recorded on a JEOL JNM AL-400 (400 MHz) spectrometer, a Bruker DRX-300 (300 MHz) spectrometer, or a Bruker DRX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, and integration. ^{13}C NMR spectra were recorded on a JEOL JNM AL-400 (100 MHz) spectrometer or a Bruker DRX-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0). Mass spectra were recorded on a Waters Micromass ZQ Mass Spectrometer with 2695 using electron spray ionization (ESI). High resolution mass spectrometry (HRMS) spectra were obtained using an Agilent 6530 Q-TOF/MS instrument. Column chromatography was carried out with Cica-reagent silica gel 60N (spherical, particle size 63-210 μm). Thin-layer chromatography (TLC) was carried out with Merck TLC plates with silica gel 60 F_{254}.

Unless otherwise noted, reagents were commercially available and were used without purification. The solvents used were purified by distillation over drying agents indicated: THF (Na/benzophenone); DMSO, DMF, MeCN (CaH_2); NMP, *n*-BuOH ($MgSO_4$); toluene ($CaCl_2$); MeOH (Mg); propylenecarbonate, propionitrile, 2MeOEtOH, *t*-BuOH, DCE, diisopropylether (MS4A)

General procedure for self-propagative Lossen rearrangement of free aromatic hydroxamic acids to primary amines.

A mixture of *N*-hydroxy-4-methylbezamide (**1a**) (0.363 g, 2.4 mmol), K_2CO_3 (0.332 g, 2.4 mmol), and DMSO (2 mL) was heated to 90 °C and stirred at that temperature for 2 h. The mixture was cooled to rt, and then treated with 2 M HCl (ca. 3 mL). After the mixture became the clear solution, 2 M NaOH (ca. 3 mL) was added and extracted with Et_2O (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et_2O 1:1) to yield the pure 4-methylaniline (**2a**) (0.253 g, 98%) as a white crystalline solid.

4-Methylaniline (2a)[26]**:** Yield 98%. White crystalline solid. IR (KBr) ν 3418, 3337, 3222, 3010, 2914, 2859, 1622, 1514, 1280, 1268, 810, 508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.51 (s, 2H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 2H).

Aniline (2b)[27]**:** Yield 96%. Pale yellow liquid. IR (neat) ν 3429, 3355, 3036, 1621, 1602, 1278, 1175, 755, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 2H), 6.69 (d, *J* = 7.8 Hz, 2H), 6.76 (t, *J* = 7.8 Hz, 1H), 7.13-7.18 (m, 2H).

2-Methylaniline (2c)[26]**:** Yield 99%. Pale brownish liquid. IR (KBr) ν 3452, 3361, 3021, 2931, 1623, 1498, 1669, 1304, 1272, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 1H), 3.59 (s, 2H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.71 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 2H).

3-Methylaniline (2d)[28]**:** Yield 99%. Pale brownish liquid. IR (neat) ν 3436, 3352, 3034, 2919, 1623, 1494, 1293, 776, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.59 (s, 2H), 6.48-6.60 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 1H).

4-*tert*-Butylaniline (2e)[29]**:** Yield 90%.brown oil. IR (neat) ν 3363, 2959, 2867, 1621, 1515, 1363, 1265, 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H), 3.55 (s, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H).

4-Methoxyaniline (2f)[26]**:** Yield 99%. White crystalline solid. IR (KBr) ν 3422, 3347, 2964, 2839, 1509, 1235, 1032, 826, 514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (s, 2H), 3.74 (s, 3H), 6.65 (d, *J* = 9.4 Hz, 2H), 6.70 (d, *J* = 9.4 Hz, 2H).

4-Chroloaniline (2g)[30]**:** Yield 90%. Gray crystalline solid. IR (KBr) ν 3472, 3382, 1616, 1494, 1288, 1181, 821, 639, 505 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 3.65 (s, 2H), 6.60 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H).

4-Bromoaniline (2h)[31,32]: Yield 92%. Gray crystalline solid. IR (KBr) ν 3474, 3382, 1612, 1489, 1286, 1286, 1180, 1069, 818, 502 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H).

4-Nitroaniline (2i)[26,30]: Yield 88%. Yellow crystalline solid. IR (KBr) ν 3482, 3360, 1631, 1587, 1471, 1299, 1114, 840, 753, 490 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.38 (s, 2H), 6.63 (d, *J* = 5.4 Hz, 2H), 8.08 (d, *J* = 5.4 Hz, 2H).

2-Iodoaniline (2j)[33]: Yield 98%. White solid. IR (KBr) ν3394, 3290, 3187, 1623, 1474, 1300, 1251, 1146, 1006, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ4.08 (s, 2H), 6.47 (t, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H).

2,6-Dimethoxyaniline (2k)[34]: Yield 98%. White solid. IR (KBr) ν3464, 3373, 2962, 1603, 1505, 1478, 1144, 766, 597 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ3.82 (s, 2H), 3.85 (s, 6H), 6.53 (d, *J* = 8.1 Hz, 2H), 6.69 (t, *J* = 8.1 Hz, 1H).

2,3-Dimethoxyaniline (2l)[35]: Yield 99%. White solid. IR (KBr) ν3466, 3369, 2938, 1615, 1322, 1265, 1133, 1089, 733 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ3.40-4.10 (br s, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 6.34 (d, *J* = 8.1 Hz, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 6.84 (t, *J* = 8.1 Hz, 1H).

3,5-Dimethylaniline (2m)[28]: Yield 97%. Brown oil. IR (neat) ν3348, 3019, 1594, 0.005, 1175, 825, 686 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ2.22 (s, 6H), 3.34-3.69 (br s, 2H), 6.63 (s, 2H), 6.42 (s, 1H).

2-Aminopyridine (2n)[36]**:** Yield 74%. Yellow solid. IR (ATR) ν 3334, 1600, 1484, 1440, 1321, 1152, 991, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (s, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.63 (t, *J* = 6.2 Hz, 1H), 7.38-7.45 (m, 1H), 8.06 (d, *J* = 5.0 Hz, 1H)

2-Aminoquinoline (2o)[37]**:** Yield 76%. Yellow solid. IR (ATR) ν 3149, 1611, 1506, 1428, 1352, 1123, 1023, 819, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ4.84 (s, 2H), 6.72 (d, *J* = 8.8 Hz, 1H), 7.22-7.30 (m, 1H), 7.53-7.68 (m, 3H), 7.88 (d, *J* = 8.7 Hz, 1H).

General procedure for self-propagative Lossen rearrangement of free aliphatic hydroxamic acids to primary amines.

A mixture of *N*-hydroxy-2-phenylacetamide (**1p**) (0.363 g, 2.4 mmol), K_2CO_3 (0.332 g, 2.4 mmol), and DMSO (2 mL) were heated to 90 °C and stirred at the temperature for 2 h. The mixture was cooled to rt, and then treated with 2M-HCl (ca. 3 mL) and stirred at the room temperature for 1 h. The reaction mixture was cooled to 0 °C, and the mixture became the clear solution. 2 M NaOH (ca. 2 mL) and Z-chloride (0.51 mL, 3.6 mmol) was added successively. After stirred for 12 h, the mixture was extracted with Et_2O (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et_2O 1:1) to yield the pure benzyl *N*–benzylcarbamate (**2p**) (0.550 g, 95%) as a white crystalline solid.

Benzyl *N*-benzylcarbamate (2p)[38]: Yield 95%. White crystalline solid. IR (KBr) ν3323, 3032, 1686, 1542, 1454, 1260, 1145, 724, 694, cm^{-1}: ^{1}H NMR (270 MHz $CDCl_3$) δ4.38 (d, *J* = 6.0 Hz, 2H), 5.07 (s, 1H), 5.13 (s, 2H), 7.26-7.35 (m, 10H).

Benzyl *N*-(2-phenylethyl)carbamate (2q)[39]: Yield 82%. White crystalline solid. IR (KBr) ν3328, 3030, 1684, 1541, 1454, 1296, 1259, 1142, 1030, 746, 697 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ2.81 (t, *J* = 6.8 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 4.77 (s, 1H), 5.09 (s, 2H), 7.16-7.34 (m, 10H).

Benzyl *N*-(cyclohexylmethyl)carbamate (2r)[40]: Yield 80%. Blown solid. IR (KBr) ν3303, 2925, 2849, 1697, 1548, 1446, 1248, 1138, 730, 694 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ0.87-1.00 (m, 2H), 1.12-1.29 (m, 2H), 1.43-1.44 (m, 1H), 1.64-1.78 (m, 6H), 3.03 (d, *J* = 6.4 Hz, 2H), 4.82 (s, 1H), 5.09 (s, 2H), 7.29-7.36 (m, 5H).

Benzyl *N*-cyclohexylcabamate (2s)[41]: Yield 98%. White solid. IR (KBr) ν3320, 2932, 2854, 1685, 1541, 1234, 1048, 758, 693 cm^{-1}: ^{1}H NMR (270 MHz, $CDCl_3$) δ1.05-1.41 (m, 4H), 1.57-1.73 (m, 4H), 1.94 (d, *J* = 5.9 Hz, 2H), 3.50 (t, *J* = 4.1 Hz, 1H), 4.63 (s, 1H), 5.08 (s, 2H), 7.29-7.38 (m, 5H).

1-Adamantanamine (2t)[42]: After 2M NaOH was added, the precipitate was collected by suction filtration. Yield 98 %. White solid. IR (KBr) ν2909, 2851, 1640, 1551, 1457, 1341, 1317, 1291 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.46-1.76 (m, 14H), 1.96 (s, 3H).

Benzyl *N*-(*cis*-8-heptadecenyl)carbamate (2u): Yield 95%. Yellow oil. IR (neat) ν 3341, 2925, 2854, 1715, 1531, 1456, 1253, 732, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ0.88 (t, *J* = 6.8 Hz, 3H), 1.27-1.30 (m, 20H), 1.49-1.66 (m, 2H), 2.01 (d, *J* = 6.0 Hz, 2H), 3.16-3.26 (m, 2H), 4.71 (s, 1H), 5.11 (d, *J* = 7.2 Hz, 2H), 5.30-5.39 (m, 2H), 7.29-7.36 (m, 5H).HRMS (ESI) *m/z* 410.3041 (410.3030 calcd for $C_{25}H_{41}NO_2Na$ [M+Na$^+$])

Benzyl N-[1-(6-methoxynaphth-2-yl)ethyl]acetamide (2x) : Yield 65%. $[\alpha]_D^{25}$ = -16.0 (c. = 1.0 in $CHCl_3$). IR (neat) ν 3287, 3059, 2950, 1685, 1540, 1318, 1249, 1223, 1058, 1028, 859, 698, 471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.55 (d, *J* = 6.4 Hz, 3H), 3.91 (s, 3H), 4.99-5.14 (m, 4H), 7.11-7.15 (m, 2H), 7.34-7.40 (m, 6H), 7.66-7.72 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ22.3, 50.6, 55.2, 66.7, 105.5, 118.9, 124.2, 124.9, 127.2, 128.0, 128.4, 128.5, 128.7, 129.3, 133.9, 136.4, 155.5, 157.6. LC-MS (ESI), found [M+Na$^+$] 358.2 (calcd, 358.1). HPLC [Chiralpak IC, *n*-hexane/2-propanol = 90 : 10, 0.5 mL/min, λ = 254 nm, retention times: (minor) 29.9 min, (major) 39.7 min].

Synthesis of 1-(6-methoxynaphth-2-yl)ethylamine hydrochloride (3).

To a solution of Cbz-protected amine **2x** (20.1 mg, 0.06 mmol) in EtOH (1 mL) was added 10% Pd-C (0.6 mg). The flask was charged with hydrogen gas and stirred for 1 h. The reaction mixture was filtered and removal of the solvent *in vacuo* to give a 1-(6-methoxynaphth-2-yl)ethylamine (11.3 mg, 94%) as a pale yellow solid. Then deprotected amine (11.3 mg) was dissolved in MeOH (0.5 mL) and 2M HCl aq. was added. Standing for 10 min at room temperature followed by removal of the solvents *in vacuo.* The precipitate was collected by suction filtration to give a 1-(6-methoxynaphth-2-yl)ethylamine hydrochloride **3** (14.2 mg, 99%) as a white solid.[21]

$[\alpha]_D^{25}$ = -23.0 (c. 0.1 in MeOH). ^{1}H NMR (270 MHz, D_2O) δ1.59 (d, *J* = 6.0 Hz), 3.80 (brs, 3H), 4.54 (d, *J* = 6.0 Hz, 2H), 7.10-7.21 (m, 2H), 7.39-7.42 (m, 1H), 7.75-7.76 (m, 3H).

K_2CO_3-mediated reaction of *p*-methylbenzohydroxamic acid in the presence of a catalytic amount of phenyl isocyanate in DMSO at room temperature

To a solution of *p*-methylbenzhydoxamic acid **1a** (0.363g, 2.4 mmol) in DMSO (2 mL) were added K_2CO_3 (0.332 g, 2.4 mmol) and phenyl isocyanate (0.013 mL, 0.12 mmol). The mixture was stirred for 24 h at room temperature, followed by 2 M HCl aq. (6 mL) and 2 M NaOH (6 mL) were added.

The mixture was extracted with Et_2O (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et_2O 1:1) to yield the *p*-toluidine **2a** (25%) and *O*-(4-methylphenylcarbamoyl)-4-methylhydroxamic acid **4a** (24%). In the case of 48 h, *p*-toluidine was obtained in 92% yield, and *O*-(4-methylphenylcarbamoyl)-4-methylhydroxamic acid **4a** was not obtained.

Synthesis of *O*-phenylcarbamoyl-4-nitrobenzhydroxamic acid 4b.

To a mixture of 4-nitrobenzhydroxamic acid **1j** (0.911g, 5.0 mmol) and K_2CO_3 (0.696 g, 5.0 mmol) in DMSO (4 mL) was added phenylisocyanate (0.543 g, 5.0 mmol). Immediately, 2 M HCl aq. (8 mL) was added followed by the precipitate was collected by suction filtration and washed by H_2O and Et_2O. The solvent was removed *in vacuo* to give a *O*-phenylcarbamoyl-4-nitrobenzhydroxamic acid **4b** (1.49 g, 99%) as a brown solid.

IR (KBr) ν 3306, 3226, 1751, 1681, 1602, 1524, 1348, 1210, 1012, 711 cm^{-1}: ^1H NMR (270 MHz, DMSO-d_6) δ 7.08 (t, J = 7.0 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 8.09 (d, J = 8.6 Hz, 2H), 8.38 (d, J = 8.6 Hz, 2H), 10.37 (s, 1H), 12.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.5, 123.3, 123.9, 128.9, 129.0, 136.7, 138.1, 150.0, 152.0. LC-MS (ESI), found [M+Na^+] 324.2 (calcd 324.1).

Acknowledgements

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23 See Supporting Information.

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