Short Synthesis of Novel Recyclable Chiral Bifunctional Thioureas from Aminoalkyl Polystyrene and their use as Organocatalysts in Stereoselective aza-Henry Reaction.

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Abstract.

A series of supported bifunctional thioureas has been prepared, in one or two steps, from commercially available aminoalkyl polystyrene resins. They differ in the length of the tether attaching the thiourea to the polymer chain, and the nature of the amino thiourea component. All the materials are able to promote stereoselective aza-Henry reaction with very good stereoselection, and they can be recycled maintaining the catalytic activity.

Introduction

The search for novel highly efficient and recoverable organocatalysts to be used in enantioselective transformations constitutes a research field of continuous interest. Two main problems are associated to organocatalytic transformations: one of them refers to the high loading of catalyst used to promote efficient transformations,[1] and the second one is related with the recovering and recycling of the catalyst[2] The most studied solution for the last problem refers to the preparation of different solid materials decorated with the catalysts.

Bifunctional ureas and thioureas are organocatalysts able to activate both the nucleophile and electrophile by non-covalent interactions,[3] and the first supported thiourea was described twenty years ago.[4] Since then, it has been reported some examples of thioureas supported on polystyrene resins,[5] and different inorganic materials,[6] increasing the easy recovering of the catalysts and the efficiency and greenness of the processes.

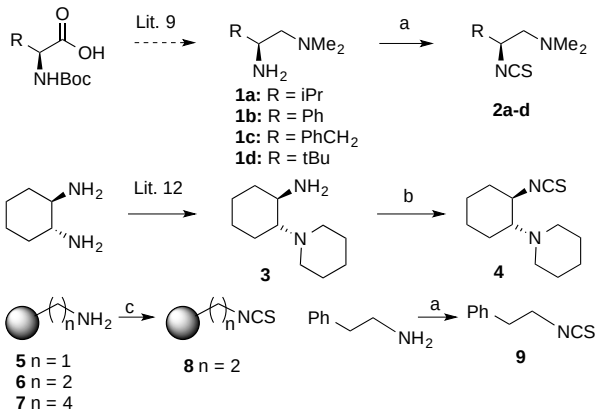
As a part of our interest in the synthesis of renewable organocatalysts for different enantioselective transformations we have recently described some polymeric chiral bifunctional thioureas prepared by both bottom-up synthesis,[7] or anchored on commercially available chlorosulfonyl polystyrene.[8] In general, the last way needs for a previous manipulation of the resins or the thiourea components to put a functionalized tether which facilitates the anchorage of the catalyst into the polymer.

Results and discussion

Chiral α-amino isothiocyanates **2a-d** were prepared from diamines **1a-d**[9] in two different ways. Diamines **1a**,**b** reacted with an ethereal solution of carbon disulfide in the presence of DCC[10] leading to isothiocyanates **2a**,**b** in moderate yields, whereas **2c**,**d** were obtained, in good yields, by reaction of diamines **1c**,**d** with carbon disulfide and TEA, followed by treatment of the reaction mixture with di-tert-butyl dicarbonate in ethanol and catalytic DMAP.[11] Isothiocyanate **4**, derived from (1*R*,2*R*)-1,2-cyclohexane diamine, was synthesized by reaction of diamine **3**[12] with thiophosgene and triethylamine in DCM at room temperature.[13]

Polymeric isothiocyanate **8** was quantitatively obtained by treatment of commercially available aminoethyl polystyrene resin **6** with thiophosgene/TEA in DCM at rt. The

effective functionalization of the polymer was determined on the basis of the analytical data of the sulfur atom as f = 1.05 mmol.g^{-1}, and it was characterized by the 2083 cm^{-1} IR band, corresponding to the –N=C=S group. For comparative purposes, isothiocyanate **9** was also prepared from phenethylamine as previously described[14] (Scheme 1).

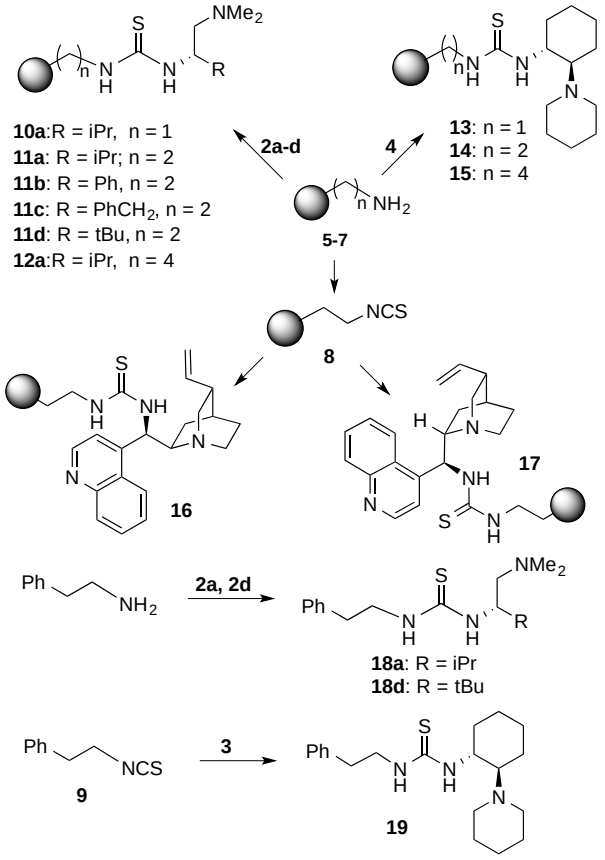


Scheme 1. *Reagents and conditions*: a) CS_2, DCC, Et_2O, 0 ºC to rt, 12h for **2a**, **b**, or 1. CS_2, Et_3N, EtOH, rt, 30 min. 2. Boc_2O, DMAP (3 mol%), EtOH, 0 ºC to rt. For **2c**, **d** and **9**. b) $CSCl_2$ (1.2 equiv), Et_3N (4 equiv), CH_2Cl_2, rt, 30 min. c) $CSCl_2$ (1.2 equiv), Et_3N (4 equiv), DCM, rt, 12h.

With isothiocyanates **2-9** in hands, we prepared a series of eleven supported, and three unsupported thioureas which differ in the length of the tether connecting the chiral appendage to the polymer, the size of the substituent at the stereogenic center at the thiourea component, and the nature of the diamine structure (Scheme 2). Supported thioureas **10**-**15** were obtained, in excellent yields, by reaction of aminomethyl- (**5**), 2-aminoethyl- (**6**), and 4-aminobutyl-polystyrene (**7**) with isothiocyanates **2a**-**d** or **6** in DCM at room temperature for 24 h. Additionally, supported thioureas **16** and **17** were prepared by condensation of polystyrene isothiocyanate **8** with commercially available (9*R*)-9-deoxy-9-aminocinchonine, and (9*S*)-9-deoxy-9-aminocinchonidine, respectively.

Unsupported thioureas **18a** and **18d** were also synthesized by reaction of 2-phenylethylamine with isothiocyanates **2a** and **2d**, derived from *L*-valine and *L*-tert-

leucine, respectively, and **19** was obtained by condensation of 2-phenylethyl isothiocyanate **9** and (1*R*, 2*R*)-1,2-cycloheanediamine-derivative **3**. All these reactions occurred with excellent yields, and the effective functionalization (*f*),[15] calculated on the basis of the analytical data for the sulfur, varies between 0.73 and 1.05 mmol g^{-1}.



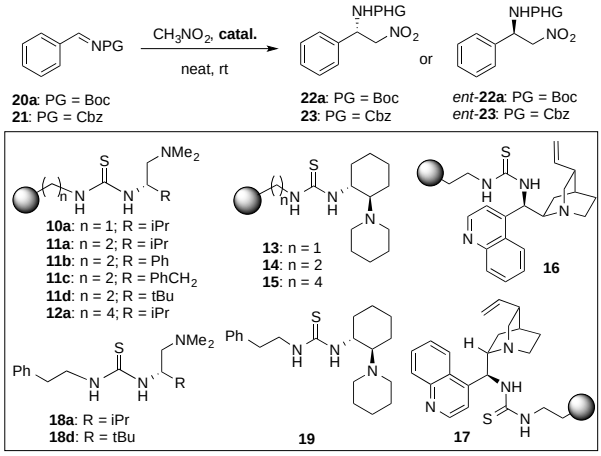
Scheme 2. Synthesis of supported and unsupported bifunctional thioureas.

The catalytic ability of the novel thioureas was tested for the stereoselective aza-Henry reaction,[16] by stirring a mixture benzaldimines **20a** or **21** and nitromethane (6 equiv) in the presence of 5 mol% of catalysts, and the results are collected in Table 1.

We first studied the influence of the length of the tether attaching the polymer and the active site of the supported materials. To that end, we tested the reaction in the presence of valine-derived catalysts **10a**, **11a**, and **12a** (entries 1-3 in Table 1), and catalysts **13-15**, derived from (1*R*, 2*R*)-cyclohexane diamine (entries 10-13 in Table 1), respectively. In both cases, no important changes in the enantioselection were observed, although the best results were obtained for the reactions catalyzed by 2-aminoethyl polystyrene-derived (n = 2) catalysts **11a** and **14**, respectively.

No special variations in the enantioselection were detected by changing the protective group in the aldimine from Boc (**22a**) to Cbz (**23**) (compare entries 2 and 4 in Table 1).

Table 1. Enantioselective aza-Henry reaction of imines with nitromethane in the presence of different catalysts.



Entry[a]	Catalyst (%)	Time (h)	Product (%)[b]	Er[c]
1	**10a** (5%)	6	**22a** (70)	86:14
2	**11a** (5%)	6	**22a** (75)	89:11
3	**12a** (5%)	6	**22a** (81)	85:15
4[d]	**11a** (5%)	6	**23** (70)	89:11
5	**11b** (5%)	7	**22a** (70)	87:13
6	**11c** (5%)	8	**22a** (62)	92:8
7	**11d** (5%)	6	**22a** (78)	93:7
8[e]	**11d** (5%)	16	**22a** (80)	92:8
9	**11d** (2%)	12	**22a** (70)	91:9
10	**13** (5%)	2.5	*ent*-**22a** (66)	91:9
11	**14** (5%)	2.5	*ent*-**22a** (64)	92:8
12	**14** (2%)	2.5	*ent*-**22a** (56)	93:7
13	**15** (5%)	2.5	*ent*-**22a** (50)	91:9
14	**16** (5%)	2.5	*ent*-**22a** (40)	81:19
15	**17** (5%)	2.5	**22a** (40)	16:84
16	**18a** (5%)	3	**22a** (65)	88:12
17	**18d** (5%)	6	**22a** (55)	91:9
18	**19** (5%)	2.5	*ent*-**22a** (90)	92:8

[a] Reactions were conducted with imine **20a** at 0.3 mmol scale in 0.1 mL of nitromethane (6 equiv). [b] Isolated yield. [c] Enantiomeric ratio determined by HPLC analysis using a chiral column, and the absolute configuration was determined by comparison of the HPLC retention time with that of literature data. [d] Reaction performed with imine **21**. [e] Reaction performed at 0 ºC.

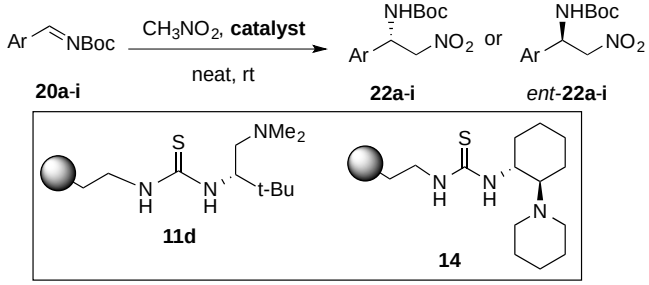
The influence of the nature of the amine component on the enantioselection was also studied, observing that the reactions promoted by thioureas **13-15**, derived from cyclohexane diamine, were more enantioselective than those promoted by thioureas derived from *L*-amino acids except for *tert*-leucine-derived thiourea **11d** (entry 7), and both catalysts are enantiocomplementary. On the contrary, cinchona-derived thioureas **16** and **17** provided only moderate enantioselection (entries 14, 15 in Table 1). The reaction temperature does not play an important role in the yield and enantioselectivity of the reaction, although increasing the reaction time (compare entry 7 versus 8 in Table 1), and the results obtained in the reactions catalyzed by unsupported soluble thioureas **18a**, **18d**, and **19** were very similar than those observed for the homologous supported ones **11a**, **11d**, and **14** (compare entries 16-18 versus 2, 7, and 11 respectively).

It is important to note that the loading of the catalyst can be reduced to 2 mol% without negligible variation in the enantioselectivity, but increasing the reaction time for catalyst **11d** (compare entries 7 versus 9, and 11 versus 12 in Table 1).

The best catalysts **11d** and **14** were selected to extend the reaction of different aldimines with nitromethane. The reactions were carried out at rt, in the presence of 5 mol% of catalyst **11d** or 2 mol% of **14**, and the results are summarized in Table 2. The results shown that the supported catalyst, derived from cyclohexane diamine **14** is more active than the tert-leucine-derived one (**11d**) because the reactions need shorter reaction times to finish. The enantioselectivities were maintained very high independently of the electronic character of the substituent at the aromatic ring of the imine, and as expected, imines with substituents with donor character (**20f**, **g**) are less reactive than those with withdrawing properties (**20b**-**e**).

The reaction also worked well for naphtaldehyde-derived imines **20h** and **20i**, leading to the addition products in good yields and enantioselectivities independently of the position of the imine group. The reaction can be scale up to 3 mmol maintaining the enantioselection. In that case, the enantiopurity of the nitroamine derivative can be improve to 98:2 by a single recrystallization of the reaction mixture in hexane-ethyl acetate (entry 18 in Table 2). Fortunately, both catalysts **11d**, and **14** were recycled for five times (entries 19-22 in Table 2) or four times (entries 23-25 in Table 2), respectively, without loss of activity.

Table 2. Aza-Henry reaction for different aldimines.

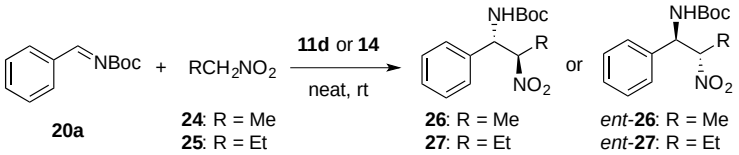


Entry[a]	Ar (Aldimine)	Catalyst (%)	t(h)	Product Yield (%)[b]	Er[c]
1	Ph (**20a**)	**11d** (5%)	6	**22a** (78)	93:7
2	Ph (**20a**)	**14** (2%)	2.5	*ent*-**22a** (56)	93:7
3	*p*-ClC_6H_4 (**20b**)	**11d** (5%)	3	**22b** (68)	92:8
4	*p*-ClC_6H_4 (**20b**)	**14** (2%)	1.5	*ent*-**22b** (65)	90:10
5	*o*-ClC_6H_4 (**20c**)	**11d** (5%)	2	**22c** (60)	90:10
6	*p*-$CF_3C_6H_4$ (**20d**)	**11d** (5%)	3	**22d** (70)	93:7
7	*p*-$CF_3C_6H_4$(**20d**)	**14** (2%)	1.5	*ent*-**22d** (80)	89:11
8	*p*-$NO_2C_6H_4$ (**20e**)	**11d** (5%)	2	**22e** (77)	91:9
9	*p*-$NO_2C_6H_4$ (**20e**)	**14** (2%)	2.5	*ent*-**22e** (85)	89:11
10	*p*-MeC_6H_4 (**20f**)	**11d** (5%)	10	**22f** (75)	92:8
11	*p*-MeC_6H_4 (**20f**)	**14** (2%)	3	*ent*-**22f** (87)	91:9
12	*p*-$MeOC_6H_4$ (**20g**)	**11d** (5%)	18	**22g** (71)	96:4
13	*p*-$MeOC_6H_4$ (**20g**)	**14** (2%)	8	*ent*-**22g** (75)	90:10
14	1-naphtyl (**20h**)	**11d** (5%)	6	**22h** (76)	90:10
15	1-naphtyl (**20h**)	**14** (2%)	8	*ent*-**22b**(80)	90:10
16	2-naphtyl (**20i**)	**11d** (5%)	7	**22i** (70)	87:13
17	2-naphtyl (**20i**)	**14** (2%)	7	*ent*-**22i** (80)	91:9
18[d]	Ph (**20a**)	**11d** (5%)	6	**22a** (50)	90:10 (98:2)[e]
19	Ph (**20a**) (2^{nd}cycle)	**11d** (5%)	6	**22a** (80)	91:9
20	Ph (**20a**) (3^{th}cycle)	**11d** (5%)	6	**22a** (71)	91:9
21	Ph (**20a**) (4^{th}cycle)	**11d** (5%)	6	**22a** (73)	90:10
22	Ph (**20a**) (5^{th}cycle)	**11d** (5%)	6	**22a** (80)	91:9
23	Ph (**20a**) (2^{nd}cycle)	**14** (2%)	2.5	*ent*-**22a** (67)	93:7
24	Ph (**20a**) (3^{th}cycle)	**14** (2%)	2.5	*ent*-**22a** (71)	93:7
25	Ph (**20a**) (4^{th}cycle)	**14** (2%)	2.5	*ent*-**22a** (67)	92:8

[a] The reactions were carried out with imines **20a-i** (0.3 mmol) and nitromethane (6 equiv) at room temperature in the presence of catalyst **11d** (0.05 equiv) or **14** (0.02 equiv). [b] Isolated yield after chromatography. [c] Enantiomeric ratio determined by HPLC analysis using a chiral column and absolute configuration was determined by comparison of the HPLC retention time with that of the literature data. [d] The reaction was carried out at 3 mmol scale. [e] Numbers in parenthesis refer to the er after one recrystallization.

Catalysts **11d** and **14** were also tested in the diastereoselective aza-Henry reaction by using nitroethane and 1-nitropropane as nucleophiles (Table 3). In both cases the reaction occurs easily leading to *anti* adducts **26** and **27** as major diastereoisomers with moderate diastereoselectivities and very good enantioselectivities. The observed enantioselectivity for the formation of the minor *syn*-diastereosisomers was only moderate.

Table 3. Stereoselective reactions of benzaldimine **20a** with nitroethane and 1-nitropropane catalyzed by **11d** and **14**.



20a

24: R = Me
25: R = Et

26: R = Me
27: R = Et

ent-**26**: R = Me
ent-**27**: R = Et

Entry[a]	Reagent	Catalyst	t(h)	Product (Yield)[b]	*anti:syn*[c]	Er[c]
1	**24**	**11d** (5%)	3	**26** (75)	83:17	93:7 (79:21)
2	**24**	**14** (5%)	2.5	*ent*-**26** (85)	80:20	95:5 (86:14)
3	**25**	**11d** (5%)	3	**27** (60)	75:25	92:8 (75:25)
4	**25**	**14** (2%)	3	*ent*-**27** (65)	84:16	95:5 (81:19)

[a] The reactions were carried out with imine **20a** (0.3 mmol) and nitroalkanes (6 equiv) at room temperature in the presence of catalyst (0.02-0.05 equiv). [b] Isolated yield after chromatography. [c] Diastereomeric and enantiomeric ratio determined by chiral HPLC; er of the minor diastereomer in parenthesis.

Conclusion

Eleven novel supported chiral bifunctional thioureas have been prepared, in one or two steps, from commercially available aminoalkyl polystyrene resins. The synthesis of polymeric materials was carried out by reaction of isothiocyanates prepared, in one step from the same amino polystyrenes, with chiral diamines, or by reaction of the parent resins with chiral amino isothiocyanates derived from natural amino acids. All these materials were used as organocatalysts in stereoselective aza-Henry reactions, leading to the addition products with very good stereoselection. The best results were obtained in the reactions promoted by tert-leucine-derived catalyst **11d**, and (1*R*, 2*R*)-

1,2-cyclohexane diamine-derived catalyst **14**. The reaction can be scaled up, and the catalysts can be recycled without loss of the catalytic activity.

Acknowledgements.

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References

[1] For a critical review on low catalyst loading in organocatalysis, see: F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev*. **2012**, *41*, 2406.

[2] For recent reviews see: a) I. R. Shaikh, *J. Catalysts*. **2014**, 1. b) G. Rajesh Krishnan, K. Sreekumar, in *"Supported and Reusable Organocatalyst"* from Comprehensive Enantioselective Organocatalysis. P. I. Dalko, Ed., Wiley-VCH.Weinheim, **2013**.

[3] For reviews on bifunctional hydrogen-bonding organocatalysis, see: a) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299. b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed*. **2006**, *45*, 1520. c) S. J. Connon, *Chem. Commun*., **2008**, 2499. d) S. J. Connon, *Synlett* **2009**, 354. e) L.-Q. Lu, X.-L.An, J.-R. Chen, W.-J.Xiao, *Synlett* **2012**, *23*, 490. f) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185.

[4] M. S. Sigmann, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.

[5] a) H. Miyabe, S. Tuchida, M. Yamauchi, Y. Takemoto, *Synthesis* **2006**, 3295. b) Y. Chuan, G. Chen, Y. Peng, *Tetrahedron Lett.* **2009**, *50*, 3054. c) J. Li, G. Yang, Y. Qin, X. Yang, Y. Cui, *Tetrahedron: Asymmetry* **2011**, *22*, 613. d) J. Li, G. Yang, Y. Cui, *J. Appl. Polym. Sci*. **2011**, *121*, 1506. e) L.Tuchman-Shukron, S. J. Miller, M. Portnoy, *Chem. Eur. J.* **2012**, *18*, 2290. f) S. Fotaras, C. G. Kokotos, G. Kokotos, *Org. Biomol. Chem.* **2012**, *10*, 5613. g) A. Puglisi, M. Benaglia, R. Annunziata, J. S. Siegel, *ChemCatChem* **2012**, *4*, 972. h) K. A. Fredriksen, T. E. Kristensen, T. Hansen, *Beilstein J. Org. Chem.* **2012,** *8*, 1126. i) P. Kasaplar, E. Ozkal, C. Rodríguez-Escrich, M. A. Pericàs, *Green Chem.* **2015**, *17*, 3122.

[6] a) P. Yu, J. He, C. Guo, *Chem. Commun.* **2008**, 2355. b) A. Puglisi, R. Annunciata, M. Benaglia, F. Cozzi, A. Gervasini, V. Bertacche, M. C. Sala, *Adv. Synth. Catal.* **2009**, *351*, 219. c) O. Gleeson, G.-L. Davies, A. Peschiulli, R. Tekoriute, Y. K. Gun'ko, S. J. Connon, *Org. Biomol. Chem.* **2011**, *9*, 7929. d) M. B. Gawande, P. S. Branco, R. S. Varma, *Chem. Soc. Rev.* **2013**, *42*, 3371. e) X. Jiang, H. Zhu, X. Shi, Y. Zhong, Y. Li, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 308.

[7] J. M. Andrés, N. De la Cruz, M. Valle, R. Pedrosa, *ChemPlusChem* **2016**, *81*, 86.

[8] a) R. Pedrosa, J. M. Andrés, D. P. Ávila, M. Ceballos, R. Pindado, *Green Chem.* **2015**, *17*, 2217. b) J. M. Andrés, M. Ceballos, A. Maestro, I. Sanz, R. Pedrosa, *Beilstein J. Org.Chem.* **2016**, *12*, 6728.

[9 R. Pedrosa , J. M. Andrés, R. Manzano, *Chem. Eur. J.* **2008**, *14*, 5116.

[10] J.-R. Chen, Y.-J. Cao, Y.-Q. Zou, F. Tan, L. Fu, X.-Y. Zhu, W.-J. Xiao, *Org. Biomol. Chem.* **2010**, *8*, 1275.

[11] H. Munch, J. S. Hansen, M. Pittelkow, J. B. Christensen, U. Boas, *Tetrahedron Lett.* **2008**, *49*, 3117.

[12] Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010,** *49*, 153.

[13] M. S. Manna, S. Mukherjee, *Chem. Sci.* **2014**, *5*, 1627.

[14] T. Kim, Y.-J. Kim, I.-H. Han, D. Lee, J. Ham, K. S. Kang, J. W. Lee, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 62.

[15] See supporting information

[16] a) E. Marqués-López, P. Merino, T. Tejero, R. P. Herrera, *Eur. J. Org. Chem.* **2009**, 2401. b) A. Noble, J. C. Anderson, *Chem. Rev.* **2013**, *113*, 2887.