N-Isopropylsulfinylimines *vs* *N-tert*-butylsulfinylimines in the stereoselective synthesis of sterically hindered amines: An improved synthesis of enantiopure (*R*)- and (*S*)-rimantadine and the trifluoromethylated analogues.

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An improved fully stereoselective synthesis of both enantiomers of rimantadine and its trifluoromethylated analogues has been developed, using *N*-isopropylsulfinylimines as starting chiral material, proving the superiority of the isopropyl group as chiral inducer over the *tert*-butyl group in the case of hindered *N*-sulfinylimines.

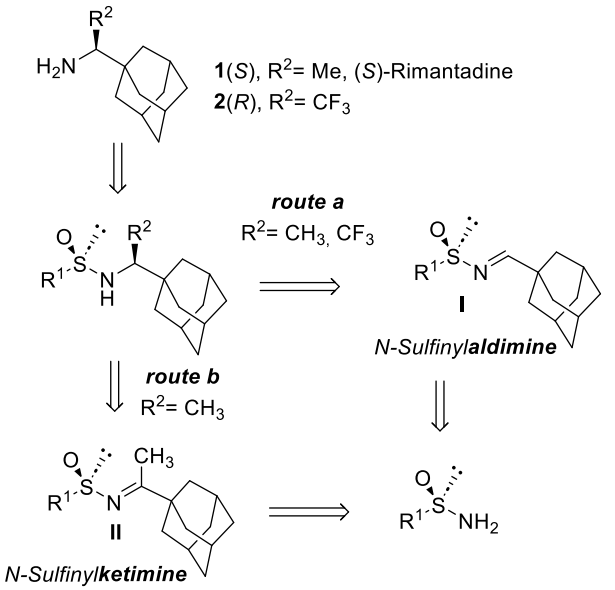
Enantiomerically pure amines are of interest as chiral building blocks for numerous biologically active compounds, as intermediates in the synthesis of pharmaceutical drugs, and as ligand in organic and organometallic catalysis.[1] The stereoselective 1,2-additions of organometallics to imines constitutes one of the most direct approaches for the synthesis of chiral amines. Interestingly, in contrast to the main chiral transformations, where a catalytic approach is always preferred to a stoichiometric one, the synthesis of chiral amine is an exception owing to the particularity of chiral *N*-sulfinylimines. Indeed, in the last two decades chiral *N*-sulfinylimines have proven to be ideal substrates for the synthesis of structurally-diverse enantiopure amines, not only for laboratory experiments but also for industrial scale production.[2]

The pioneering work of Davis group at mid-90s, using *p*-tolylsulfinilimine, demonstrated the great potential of the sulfinylimime approach where the sulfinyl group plays the triple role of chiral auxiliary, activating the CN bond, and an easily removable amine's protective group.[3] However, the real breakthrough in the field came with the use of the bulkier *N-tert*-butylsulfinylimines, synthesized for the first time by Garcia-Ruano, Fernández and col. in 1996[4] and extensively developed by Ellman, one year later.[5] The development of highly efficient methods for the synthesis of the starting *N-tert*-butanesulfinamide, currently commercially available in both enantiomeric forms, and known as Ellman's reagent, contributed to the great success of the approach, as evidenced by its innumerable applications described in the literature.[2] More recently, we introduced the *N*-isopropylsulfinylimines as an alternative intermediate to both *tert*-butyl and *p*-tolylsulfinylimines. The advantage of this chiral controller is based on its ability to induce a greater chiral discrimination than the *p*-tolylsulfinyl group and a higher reactivity than the *tert*-butylsulfinyl group, while maintaining or even exceeding the chiral induction of the process. The usefulness of the isopropylsulfinyl group was demonstrated as chiral organcatalyst in the allylsilylation of hydrazones[6] and as chiral inductor in the enantioselective synthesis of various trifluoromethyl aryl amines including the trifluoromethyl analogue of the calcimimetic drug R-(+)-NPS R-568.[7] The isosteric substitution of hydrogen by fluoride is of special interest in the design of new drugs, with a critical role and impact in drug potency, often significantly improving their pharmacological properties.[8] Guided by our interest in the synthesis of trifluoromethylated derivatives of biological relevance,[6-9] we became interested on Rimantadine. Rimantadine, 1-(1'-adamantyl)ethylamine, an antiviral used in the treatment of type A influenza by inhibiting proton conductance of the M2 ion channel of the virus,[10] is also used as an antiparkinsonian drug thanks to its NMDA antagonistic properties.[11] Rimantadine was approved by the Food and Drug Administration (FDA) in 1994 and commercialized as a racemic mixture. Currently, rimantadine is no longer clinically used due to the loss of its therapeutic efficacy, as a consequence of the preponderance of resistant viral strains. Surprisingly, although the antiviral effect of rimantadine and analogues has been known for more than four decades, the study of the relative activity of the two enantiomers at the molecular level was only addressed in 2016. Although it is known that *in vivo* both enantiomers of rimantadinne has the same therapeutic efficacy, the reported *in-vitro* results are controversial. Solid state NMR and molecular dynamics studies conducted very recently, and for the first time, suggest that (*R*)-rimantadine enantiomer binds more strongly than (*S)* enantiomer to the M2 channel.[12] However,

functional assays supported by theoretical and by ITC studies showed, at the contrary, that both enantiomers have the same affinity for the M2 channel.[13]

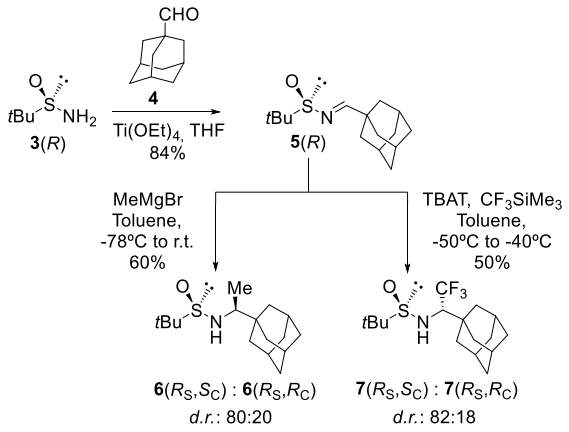
Based on these premises and due to the structural simplicity of rimantadine and its interesting mode of action at the molecular level, there is a continuing interest in developing analogues of rimantadine to combat the threat that continues to present Influenza.[14] Recently, various procedures have been developed to access both enantiopure (*R*)- and (*S*)-rimantadine, such as the optical resolution of the commercially available racemic rimantadine,[15] or the application of enzymatic methods for the reductive amination of methyl adamantyl ketone.[16] However, until now there is only one approach, recently reported, for the stereoselective synthesis of deuterated rimantadine enantiomers.[12] In this paper we present our methodology to the enantioselective synthesis of both enantiomers of rimantadine, **1**(*R*) and **1**(*S*), as well as their corresponding trifluoromethylated analogues, **2**(*R*) and **2**(*S*).

A retrosynthetic analysis of enantiopure (*R*)- or (*S*)-rimantadine shows that both enantiomers (R^2=Me, Scheme 1) could be prepared by nucleophilic addition of methyl Grignard to the adequate *N*-sulfinylaldimine **I** (*route a*, Scheme 1), or by stereoselective reduction of C-N double bond of the *N*-sulfinylketimine **II** (*route b*, Scheme 1). Taking into accounts our interest in developing a methodology that allows the preparation of not only enantiopure rimantadine but also its trifluoromethyl analogues, route (a) seemed to be most appropriate.



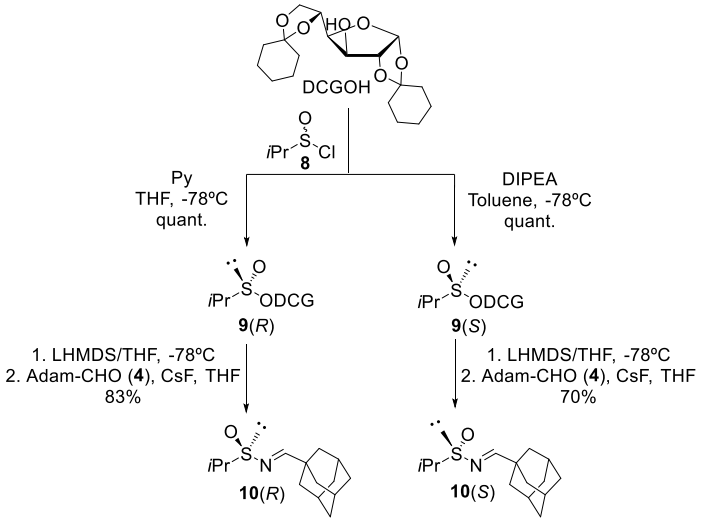
Scheme 1. Retrosynthetic scheme of enantiopure (*R*) or (*S*)-rimantadine and analogs.

Commercially available Ellman´s sulfinamides, (*R*)- and (*S*)-*tert*-butylsulfinamide (**3**(*R*)**,** R^1 = *t*Bu, Scheme 1) provides a fast and direct access to the corresponding enantiomeric sulfinylaldimines, **5**(*R*) and **5**(*S*) respectively, by condensation with 1-adamantyl carboxaldehyde **4**, Scheme 2. Thus, oxidation of 1-(adamantyl)methanol to the corresponding aldehyde, followed by condensation with (*R*)-*N*-*tert*-buthylsulfinamide **3**(*R*), produced the (*R*)-*N*-(adamantan-1-ylmethylidene) *tert*-butylsulfinylaldimine **5**(*R*). This aldimine was treated with methyl Grignard at -78°C and the reaction was left to rise to r.t., to give the addition product as a mixture of both diastereomers **6**(R_S,S_C) and **6**(R_S,R_C) in moderate chemical yield (60%) and diastereomeric ratio, (80:20 *d.r.*) (Scheme 2). This result can be rationalized by invoking the steric hindrance of the *tert*-butyl and adamantyl groups, which forces on one hand to raise the temperature so that the reaction takes place and on the other, to promote the formation of *N*-(adamant-1-ylmethyl) *tert*-butanesulfinamide via competitive reduction of the imine.[17] A similar behaviour was observed in the addition of Ruppert-Prakash's to the *tert*-butylsulfinylaldimine **5**(*R*), yielding the corresponding trifluoromethylated diastereomers **7**(R_S,R_C) and **7**(R_S,S_C), with low chemical yield (50%) and only moderate diastereoselectivity (82:18 *d.r.*), (Scheme 2).



Scheme 2. Nucleophilic additions to *N*-*tert*-butylsulfinylaldimine **5**(*R*).

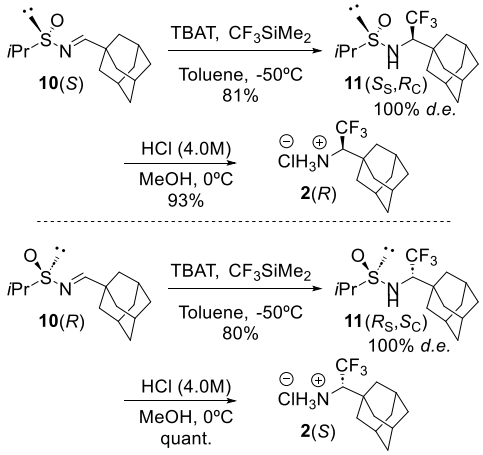
In light of these results we decided to contrast the behavior of *N*-isopropylsulfinilimines in the synthesis of the challenging rimantadine enantiomers as representative of sterically hindered amines. (*R*)- and (S)-*N*-(adamantan-1-ylmethylidene) isopropylsulfinylaldimine, **10**(*R*) and **10**(*S*), were prepared in a two-step one-pot procedure by reaction of LHMDS with the corresponding isopropylsulfinate **9**(*S*) and **9**(*R*), respectively, followed by condensation with 1-adamantylcarboxaldehyde **4** in THF, in the presence of CsF. The isopropylsulfinylating agents **9**(*S*) and **9**(*R*) were prepared formerly as previously described, from dicyclohexylidene-D-glucose (DCGOH) and isopropylsulfinyl chloride **8** as starting materials by the diastereodivergent "DAG methodology" (scheme 3).[18]



Scheme 3. Diastereodivergent synthesis of *N*-isopropylsulfinylaldimines **10**(*S*) and **10**(*R*).

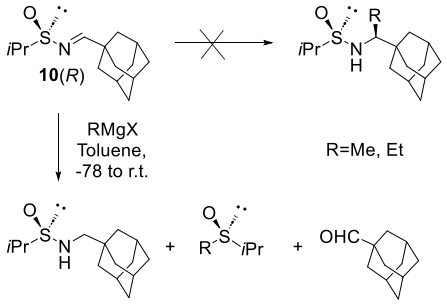
Starting with the trifluoromethylated analogues, the condensation of Ruppert-Prakash´s reagent with isopropylsulfinylimines **10**(*S*) was accomplished in toluene and the temperature was maintained at -50 °C. ^{1}H and ^{19}F NMR analysis of the crude mixture show that the reaction takes place with a 50% conversion and a total diastereoselection in favor of the trifluoromethylated sulfinamide **11**(S_S,R_C) (Scheme 4). Fortunately, the trifluoromethylated sulfinamide obtained was easily purified by flash chromatography and the unreacted sulfinylimine recovered and reused. Raising the temperature has a beneficial effect on the reaction conversion (100%), in detriment of the diastereoselection. As it has been stated in other similar substrates, the stereochemical outcome of the addition of the trifluoromethyl group can be rationalized by a non-chelated Cram model with the approach of the nucleophile on the less hindered *si* face of the C-N double bond. Desulfinylation of *N*-sulfinamide **11**(S_S,R_C) with 4N HCl in methanol at 0°C provided the corresponding trifluoromethylated rimantadine hydrochloride analogue **2**(*R*). Following a similar

route, starting from the *N*-sulfinylimine **11**(R_S,S_C) the enantiomeric trifluoromethylated analogue of (*S*)-rimantadine hydrochloride was also obtained (Scheme 4).



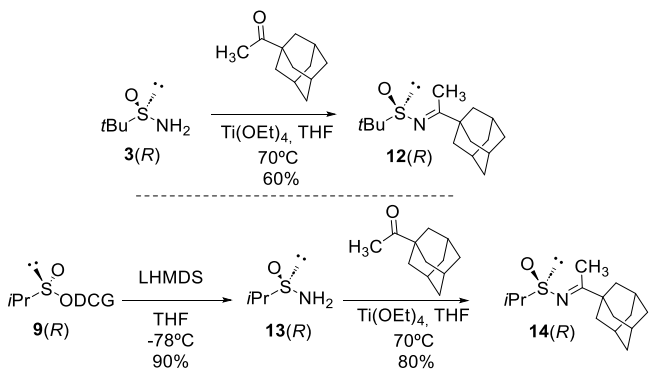
Scheme 4. Synthesis of enantiopure trifluromethylated rimantadine analogues **2**(*R*) and **2**(*S*).

In the case of rimantadine and homologues, the reaction of *N*-isopropylsulfinylimine **10**(*R*) with the Grignard reagent (R= Me or Et) did not yield the expected addition products to the double bond. Instead, a mixture of products was obtained as a result of the reduction of the imine, together with the nucleophilic attack of Grignard[17] reagent on sulfinyl sulfur atom[4] (Scheme 5). Unfortunately, the addition of a Lewis acid ($BF_3.OEt_2$) as an additive did not improve the result.[19]



Scheme 5. Reaction products by treating *N*-sulfinylimine **10**(*R*) with grignard reagents.

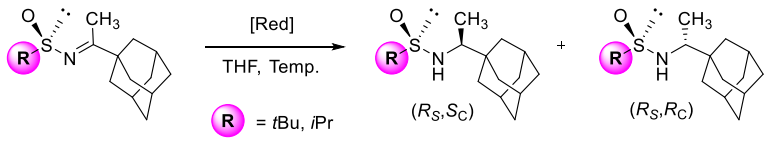
At this point, we, therefore, decided to evaluate route b (Scheme 1) for the synthesis of both enantiomers of rimantadine, using *N*-isopropylsulfiniylketimines as starting intermediates. The advantage of this approach lies in the possibility of obtaining the desired enantiomer of rimantadine through the appropriate choice of the reducing agent, through a diastereodivergent process. Both, *tert*-butyl and isopropylsulfinylketimines **12**(*R*) and **14**(*R*) were prepared as indicated in Scheme 6, by condensation of the methyl adamanthyl ketone with the corresponding alkylsulfinamide, in the presence of titanium tetraethoxide.



Scheme 6. Synthesis of N-sulfinylketimines **12**(*R*) and **14**(*R*).

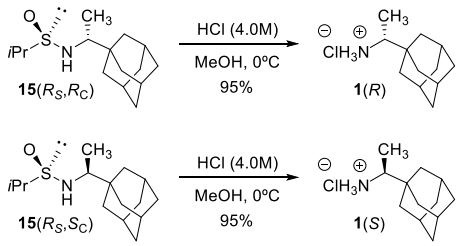
The reduction of *N*-*tert*-butylsulfinylketimine **12**(*R*) with L-selectride yielded the sulfinamide **6**(R_S,S_C) as the major diastereomer in high chemical yield and 80% *d.e.*. When DIBAL was used as the reducing agent, sulfinamide **6**(R_S,R_C) was obtained with 92% chemical yield and 75% d.e. In both cases a chromatographic separation was necessary to obtain the diastereomerically pure sulfinamides (Table 1). Interestingly, when *N*-isopropylsulfinylketimine **14**(*R*) was tested as starting material, the stereoselectivity of the process was improved significantly. Despite the lower steric volume of the isopropyl compared to the *tert*-butyl group, the reduction of *N*-isopropylsulfinylimine with L-selectride or DIBAL took place in a complete stereoselective manner, yielding sulfinamides **15**(R_S,S_C) and **15**(R_S,R_C), respectively, as a unique diastereomer, with good chemical yields (Table 1).

Table 1. Diastereodivergent reduction of *N*-*tert*-butyl- and *N*-isopropyl-sulfinylketimines, **12**(*R*) and **14**(*R*).



Entry	R	Imine	[Red]	Temp	Sulfinamide	d.r. (%) (R_S,S_C) : (R_S,R_C)	Yield (%)
1	*t*Bu	**12**(*R*)	L-Selectride	-78°C to -40°C	**6**(R_S,S_C)	90 : 10	93
2	*t*Bu	**12**(*R*)	DIBAL	-78°C	**6**(R_S,R_C)	13 : 87	92
3	*i*Pr	**14**(*R*)	L-Selectride	-78°C to -40°C	**15**(R_S,S_C)	**100 : 0**	70
4	*i*Pr	**14**(*R*)	DIBAL	-78°C	**15**(R_S,R_C)	**0 : 100**	90

Thus, both enantiomers of rimantadine, **1**(*R*) and **1**(*S*), were easily obtained as the corresponding hydrochloride salt, in enantiopure form, by desulfinylation of isopropylsulfinamides **15**(R_S,S_C) and **15**(R_S,R_C), respectively with HCl 4N (Scheme 7). Thereby, we have developed an improved totally stereoselective synthesis for both enantiomers of rimantadine and for their trifluoromethyl analogues using *N*-isopropylsufinylimines as chiral starting materials.



Scheme 7. Synthesis of enantiopure (*R*)- and (*S*)-rimantadine, **1**(*R*) and **1**(*S*).

In summary, we have reported in this work a comparative study on the stereoselective synthesis of sterically challenging rimantadine and analogues using *N*-isopropylsulfinylimines and *tert*-butylsulfinylimines as chiral intermediate. The *N*-isopropylsulfinyl group has demonstrated its preeminence over the *tert*-butylsulfinyl one both in the nucleophilic additions of trifluoromethyl anions on the sulfinylaldimines, and in the diastereoselective hydrogenation of the corresponding sulfinyl ketimines. These *N*-isopropylsulfinylimines can be easily prepared in a diastereodivergent manner using the "DAG methodology". The present work represents an improved fully stereoselective synthesis of both enantiomers of rimantadine and its trifluoromethylated analogues.

Further application of the protocol in the preparation of pharmacologically and synthetically relevant enantiopure sterically hindered amines is underway.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 R. Bloch, *Chem. Rev.* 1998, **98**, 1407; N. Hermanns, S. Dahman, C. Bolm and S. Braese, *Angew. Chem., Int. Ed.* 2002, **41**, 3692; C. H. Senanayake, D. Krishnamurthy, Z. H. Lu, Z. Han and I. Gallou, *Aldrichim. Acta*. 2005, **38**, *93*; D. Morton and R. A. Stockman, *Tetrahedron*. 2006, **62**, 8869; F. A. Davis, P. Zhou and B. C. Chen, *Chem. Soc. Rev.* 1998, **27**, 13; J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.* 2002, **35**, 984; J. A. Ellman, *Pure. Appl. Chem.* 2003, **75**, 39.

2 M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.* 2010, **110***,* 3600; G.-Q. Lin, M.-H. Xu, Y. W. Zhong and X. W. Sun, *Accounts of Chemical Research*, 2008, **41**, 831; V. Farina, J. T. Reeves, C. H. Senanayake and J. J. Song, *Chem. Rev.* 2006, **106**, 2734; P. D. Smith, M. A. Graham, R. H. Munday, C. S. Donald, T. M. McGuire and R. E. Kyne Jr. (2016) Chapter 14: Asymmetric Methods and Their Use in the Pharmaceutical Industry. D. Blakemore, P. Doyle and Y. Fobian (Ed.). In *RSC Drug Discovery Series No. 53 Synthetic Methods in Drug Discovery: Volume 2* . The Royal Society of Chemistry.

3 F. A. Davis, R. E. Reddy, J.M. Szewczyk and P. Portonovo, *Tetrahedron Lett.* 1993, **34**, 6229; P. Zhou, B. C. Chen and F.A. Davis, *Tetrahedron* 2004, **60**, 8003; F.A. Davis, *J. Org. Chem.,* 2006, **71**, 8993.

4 J. L. García Ruano, I. Fernandez, M. Prado and A. Alcudia, *Tetrahedron: Asymmetry*, 1996, **7**, 3407.

5 G. Liu., D. A. Cogan and J. A. Ellman.*J. Am. Chem. Soc.* 1997, **119**, 9913.

6 I. Fernández, V. Valdivia, B. Gori, F. Alcudia, E. Álvarez and N. Khiar, *Org. Lett*., 2005, **7**, 1307.

7 I. Fernández, V. Valdivia,A. Alcudia,A. Chelouan and N. Khiar, *Eur. J. Org. Chem*., 2010, 1502; I. Fernandez, V. Valdivia and N. Khiar**,** *J. Org. Chem.*, 2008, **73**, 745; I. Fernandez, B. Gori, F. Alcudia and N. Khiar, *Phosphorus, Sulfur and Silicon and the Related Elements*, 2005, **180**, 1511.

8 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev*. 2008, **37**, 320; K. Drlica and M. Malik, *Curr. Top. Med. Chem.*, 2003, **3**, 249; J. P. Begué and D. Bonnet-Delpon, *J. Fluorine Chem*., 2006, **127**, 992; C. Isanbor and D. O’Hagan, *J. Fluorine Chem*., 2006, **127**,303; K. L. Kirk, *J. Fluorine Chem*., 2006, **127**, 1013; K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; J. A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119; J. Gawronski, N. Wascinska and J. Gajewy, *Chem. Rev*., 2008, **108**, 5227.

9 L. G. Borrego, R. Recio, M. Alcarranza, N. Khiar and I. Fernandez, *Adv. Synth. Catal.* 2018, **360**, 1273; V. Valdivia, I. Fernandez and N. Khiar, Org. Biomol. Chem. 2014, **12**, 1211.

10 C. Wang, K. Takeuchi, L. H. Pinto and R. A. Lamb, *J. Virol.*, 1993, **67**, 5585; I. V. Chizhmakov, F. M. Geraghty, D. C. Ogden, A. Hayhurst, M. Antoniou and A .J. Hay, *J. Physiol.*, 1996, **494**, 329; F. G. Hayden, *Antiviral Res.,* 1985, **5**, 229.

11 L. Wanka, K. Iqbal and P. R. Schreiner, *Chem. Rev.*, 2013, **113**, 3516; T. P. Stockdale and C. M. Williams, *Chem. Soc. Rev.,* 2015, **44**, 7737; C. Singer, S. Papapetropoulos, M. A. Gonzalez, E. L. Roberts and A. Lieberman, *Mov. Disord.,* 2005, **20**, 873.

12 A. K. Wright, P. Batsomboon, J. Dai, I. Hung, H. X. Zhou, G. B. Dudley and T. A. Cross, *J. Am. Chem. Soc., 2016,* **138**, 1506.

13 A. Drakopoulos, C. Tzitzoglaki, C. Ma, K. Freudenberger, A. Hoffmann, Y. Hu, G. Gauglitz, M. Schmidtke, J. Wang and A. Kolocouris, *ACS Med. Chem. Lett.*, 2017, **8**, 145; A. Drakopoulos, C. Tzitzoglaki, K. McGuire, A. Hoffmann, A. Konstantinidi, D. Kolokouris, C. Ma, K. Freudenberger, J. Hutterer, G. Gauglitz, J. Wang, M. Schmidtke, D. D. Busath and A. Kolocouris, *ACS Med. Chem. Lett.*, 2018, **9**, 198.

14 N. Y. Kuznetsov, R. M. Tikhov, I. A. Godovikov, M. G. Medvedev, K. A. Lyssenko, E. I. Burtseva, E. S. Kirillovab and Y. N. Bubnov, *Org. Biomol. Chem.*, 2017, **15**, 3152; J. L. Thomaston, N. F. Polizzi, A. Konstantinidi, J. Wang, A. Kolocouris and W. F. DeGrado, *J. Am. Chem. Soc.,* 2018, **140**, 15219; Z. Fan, S. Shu, J. Ni, Q. Yao, A. Zhang, *ACS Catal*., 2016, **2**, 769.

15 J. Han, R. Takeda, T. Sato, H Moriwaki, H. Abe, K. Izawa, V. A. Soloshonok, *Molecules* 2019, **24**(9), 1828.

16 S. K. Au, B. R. Bommarius, A. S. Bommarius, ACS Catal. 2014, **4**, 11, 4021; B. R. Bommarius, M. Schürmannb, A. S. Bommarius, Chem. Commun., 2014, 50, 14953.
17 D. R. Dragoli, M. T. Burdett and J. A. Ellman, *J. Am. Chem. Soc.,* 2001, **123**, 10127; J. Rong, J. F. Collados, P. Ortiz, R. P. Jumde, E. Otten and S. R. Harutyunyan, *Nature Communications,* 2016, **7**, 13780 R. P. Jumde, F. Lanza, M. J. Veenstra and S. R. Harutyunyan, *Science,* 2016, **352**, 433; A. Kumar and A. G. Samuelson, *Chem. Asian J.* , 2010, **5**, 1830.
18 I. Fernandez, N. Khiar, J. M. Llera and F. Alcudia, *J. Org. Chem.,* 1992, **57,** 6789; N. Khiar, I. Fernández and F. Alcudia, *Tetrahedron Lett.,* 1994, **35,** 5719; N. Khiar, C. S. Araujo, F. Alcudia and I. Fernández, *J. Org. Chem.,* 2002, **67**, 345; N. Khiar, F. Alcudia, J. L. Espartero, L. Rodríguez and I. Fernández, *J. Am. Chem. Soc.*, 2000, **122**, 7598.
19 Z. Han, D. Krishnamurthy, D. Pflum, P. Grover, S. A. Wald and C. H. Senanayake, *Org. Lett*., 2002, **4**, 4025; Z. Han, D. Krishnamurthy and C. H. Senanayake, *Organic Process Research & Development* 2006, **10**, 327.