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Catalytic asymmetric synthesis of enantioenriched α -deuterated pyrrolidine derivatives†

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The recent promising applications of deuterium-labeled pharmaceutical compounds have led to an urgent need for the efficient synthetic methodologies that site-specifically incorporate a deuterium atom into bioactive molecules. Nevertheless, precisely building a deuterium-containing stereogenic center, which meets the requirement for optimizing the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of chiral drug candidates, remains a significant challenge in organic synthesis. Herein, a catalytic asymmetric strategy combining H/D exchange (H/D-Ex) and azomethine ylide-involved 1,3-dipolar cycloaddition (1,3-DC) was developed for the construction of biologically important enantioenriched α -deuterated pyrrolidine derivatives in good yields with excellent stereoselectivities and uniformly high levels of deuterium incorporation. Directly converting glycine-derived aldimine esters into the deuterated counterparts with D₂O via Cu(I)-catalyzed H/D-Ex, and the subsequent thermodynamically/kinetically favored cleavage of the α -C–H bond rather than the α -C–D bond to generate the key *N*-metallated α -deuterated azomethine ylide species for the ensuing 1,3-DC are crucial to the success of α -deuterated chiral pyrrolidine synthesis. The current protocol exhibits remarkable features, such as readily available substrates, inexpensive and safe deuterium source, mild reaction conditions, and easy manipulation. Notably, the synthetic utility of a reversed 1,3-DC/[H/D-Ex] protocol has been demonstrated by catalytic asymmetric synthesis of deuterium-labelled MDM2 antagonist idasanutlin (RG7388) with high deuterium incorporation.

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Introduction

Deuterium as one of the readily accessible and nonradioactive atoms plays crucial roles in life science because of its ability to promote the discovery and development of drugs,^{1–4} to study the reaction mechanisms,^{5,6} and to be as an ideal internal standard for mass spectrometry.⁷ Particularly, incorporating a deuterium atom into the stereogenic center of a chiral drug candidate can not only stabilize its structure^{8–12} but also improve the metabolic profile.^{13,14} For example, the deuterated analogue of (–)-CC-122, a compound currently in human clinical trials for hematological cancers and solid tumors, exhibits higher *in vitro* anti-inflammatory and *in vivo* antitumorigenic effects with the enhanced configuration stability.^{8,9} To suppress the disfavored epimerization of telaprevir without losing activity against the hepatitis C virus NS3-4A protease, the proton at the easily-epimerized stereogenic center was replaced with deuterium.¹⁰

The incorporation of a deuterium-containing stereogenic center into erythromycin B led to a remarkable reduction of acid-promoted enol ether formation without compromising the antibacterial effect.¹¹ The enantioenriched 5-deuterated (*R*)-pioglitazone proves to be a better therapeutic agent than non-deuterated pioglitazone and racemic mixtures of deuterated counterparts (Fig. 1).¹²

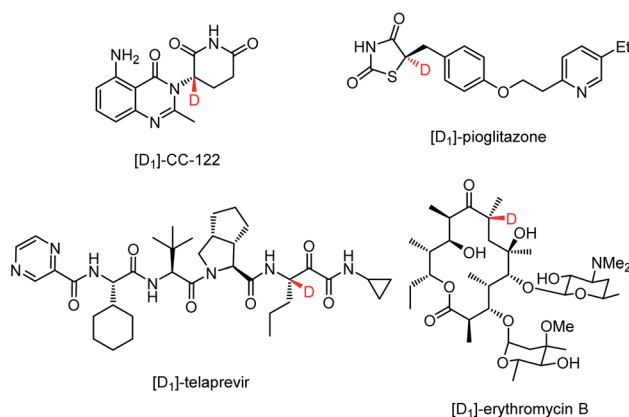


Fig. 1 Representative drug molecules bearing a deuterium-containing stereogenic center.

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Accordingly, much attention has been paid to exploit various methods for the incorporation of a deuterium atom into the stereogenic center of chiral pharmaceutical molecules or their key building blocks.^{15–21} Catalytic asymmetric synthesis, as one of the most straightforward approaches towards this goal, mainly focuses on asymmetric reduction and asymmetric deuteration of prochiral compounds^{22–30} (Scheme 1a). In contrast, catalytic asymmetric 1,3-dipolar cycloaddition reactions,^{31–35} occupying an important position in the field of organic synthesis and medicinal chemistry, have never been documented to install a deuterium-containing stereogenic center in heterocyclic adducts presumably due to the difficulty and unavailability of generating the corresponding deuterium-containing starting materials or key intermediates. Therefore, developing a novel synthetic strategy capable of precisely incorporating a deuterium-containing stereogenic center into biologically active and therapeutically-relevant heterocyclic scaffolds *via* a catalytic asymmetric cycloaddition reaction is of great significance and urgent demand.

On the other hand, optically active pyrrolidines are prevalent core structures found in many biologically active natural products and pharmaceutical molecules.^{36–38} However, only sporadic studies on the preparation of deuterated counterparts have been reported so far.^{39,40} In 1994, Beak and co-workers disclosed a sequential asymmetric deprotonation–deuteration of *N*-Boc-pyrrolidine in the presence of excess amount of (–)-sparteine, affording enantioenriched α -deuterated *N*-Boc-pyrrolidine using MeOD as the electrophile and deuterium source.³⁹ In another example, based on the modified Pieters's protocol,²¹ the team of Roche documented that stereoretentive α -deuteration of L-proline could be achieved using ruthenium on a carbon catalyst with deuterium oxide as the deuterium reagent.⁴⁰ Despite these advances, such methods suffered from harsh reaction conditions,

non-catalytic asymmetric process or extremely narrow substrate scope, which would limit their practical application.

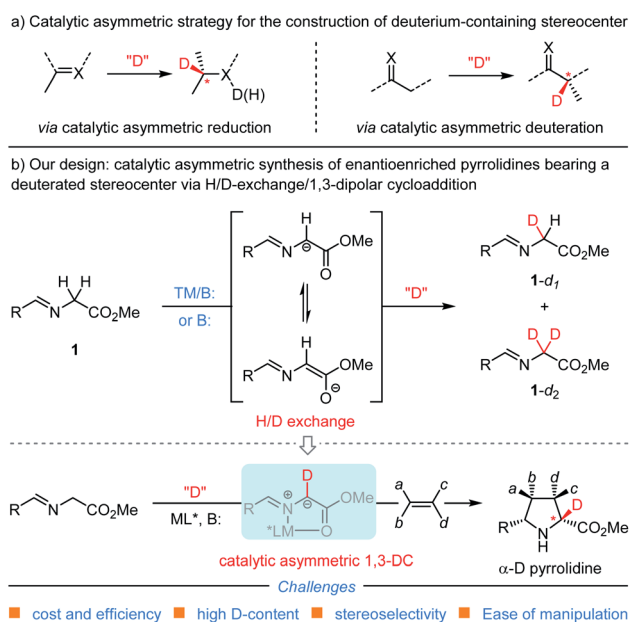
In view of the importance of deuterium-labelled chiral N-heterocycles and our continuing interest in the catalytic asymmetric construction of enantioenriched pyrrolidine derivatives with azomethine ylide,^{31,41,42} we envisioned that merging the H/D-exchange (H/D-Ex) protocol¹⁵ with the 1,3-dipolar cycloaddition reaction would meet this great challenge in a catalytic asymmetric manner and exactly cater for the ever-growing demand of deuterated bioactive heterocyclic molecules in the pharmaceutical industry.⁴³ As shown in Scheme 1b, we proposed that base-promoted and/or transition metal-catalyzed H/D-exchange of readily available glycine-derived aldimine ester with certain deuterium reagent would deliver the corresponding deuterated intermediate **1-d_n** (*n* = 1 or 2);^{44,45} the deuterated aldimine ester could coordinate with the transition-metal cation to form the key *N*-metallated azomethine ylide bearing a deuterium atom at the α -position. Subsequently, catalyst-controlled asymmetric cycloaddition of the generated *D*-azomethine ylide with dipolarophiles provides α -deuterated enantioenriched pyrrolidine derivatives. While this reaction design is conceptually straightforward, there are still some significant challenges associated with this proposal: (1) driving keto–enol tautomerization towards the deuterated intermediate **1-d_n** could be theoretically achieved by the formation of a slightly more stable C–D bond *versus* the C–H bond and by adding a large excess of certain polar deuterium reagent,⁴⁶ nonetheless, we cognized that such a thermodynamic process could be complicated by the level of deuterium-enrichment of aldimine esters and the ensuing de-deuteration or de-protonation to form the key *N*-metallated *D*-azomethine ylides with metal cations; (2) whether or not the employed polar deuterium reagent deteriorates the efficiency and diastereo-/enantioselectivity control of transition metal-catalyzed asymmetric 1,3-dipolar cycloaddition, since less polar and anhydrous solvents, such as dichloromethane, toluene or tetrahydrofuran, were commonly used in the established catalytic systems.

Herein, we report the development of an efficient synthesis of α -deuterated enantioenriched pyrrolidine derivatives *via* the strategy of combining H/D-exchange with catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. This protocol enables us to directly convert glycine derived aldimine esters to the deuterated counterparts employing relatively safe, low-cost and operationally convenient D₂O as the deuterium source under mild reaction conditions, and therefore provides a facile access to α -deuterated chiral pyrrolidines with high functionality, multiple stereocenters and uniformly high levels of deuterium incorporation for the first time.

Results and discussion

Reaction development and optimization

We initiated our investigations into the H/D-exchange performance of glycine-derived aldimine ester. In order to get insight into the H/D exchange process of aldimine ester **1a**, a series of ¹H NMR experiments were carried out with inexpensive and easy to handle D₂O as the deuterium reagent in the presence of



Scheme 1 Strategies for catalytic asymmetric construction of a deuterium-containing stereocenter.



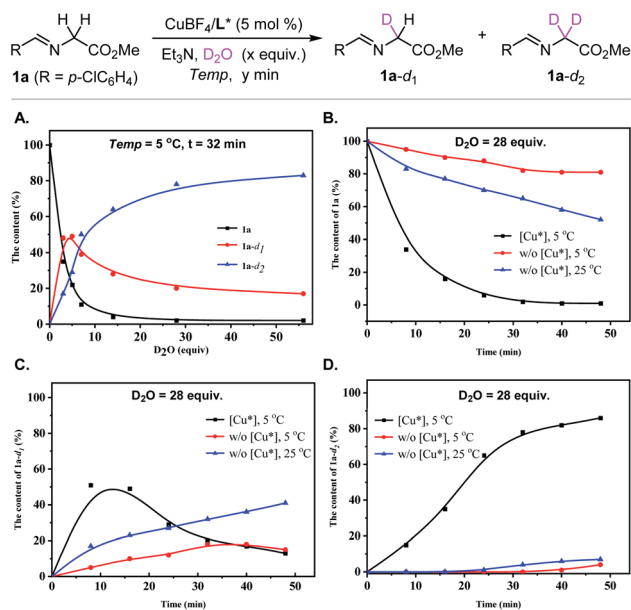


Fig. 2 ¹H NMR studies on the level of deuterium incorporation of aldimine ester **1a** with D₂O. (A) Monitoring the content of aldimine ester **1a**, **1a-d₁** and **1a-d₂** when the different amount of D₂O was used. (B) Studying the effect of reaction parameters such as chiral copper complex, reaction time and temperature on the content of aldimine ester **1a**. (C) Studying the effect of reaction parameters such as chiral copper complex, reaction time and temperature on the content of intermediate **1a-d₁**. (D) Studying the effect of reaction parameters such as chiral copper complex, reaction time and temperature on the content of intermediate **1a-d₂**.

a catalytic amount of chiral metal complex Cu(I)/(S)-TF-BiphamPhos as the catalyst and Et₃N as the base.⁴² As shown in Fig. 2A, along with the addition of the increased amount of D₂O (monitored with ¹H NMR at the indicated time intervals with 3, 5, 7, 14, 28 and 56 equiv. of D₂O, respectively, see the ESI† for details), the starting material aldimine ester **1a** was fast consumed and converted into two deuterated intermediates **1a-d₁** and **1a-d₂**, and the content of intermediate **1a-d₁** showed a fast increase and then a slow decrease in this H/D exchange process. The whole deuterium enrichment of aldimine ester **1a** improved gradually with the increased excess of D₂O. When the amount of D₂O was increased up to 28 equivalents, the ratio of the two species **1a-d₁** and **1a-d₂** tends to be stable. However, the complete α-deuteration of **1a** cannot be reached even with 56 equivalents of D₂O. The ratio of **1a** and two deuterated species **1a-d₁** and **1a-d₂** did not show any remarkable changes when the amount of D₂O was increased from 28 equiv. to 56 equiv., and the resulting mixture still contained a considerable amount of **1a-d₁** and a small amount of **1a**.

Furthermore, the effect of other reaction parameters, such as chiral copper complex, temperature and time, on the H/D exchange performance was also investigated with 28 equiv. of D₂O being added. It is worth noting that metal complex Cu(I)/(S)-TF-BiphamPhos significantly promotes the H/D exchange of aldimine ester **1a**. As shown in Fig. 2B–D, removing the chiral copper complex from the above condition seriously decayed the rate of H/D-exchange. A comparative H/D-exchange level could

not be reached even with a prolonged reaction time or at an elevated reaction temperature in the absence of the copper complex. These control experimental results revealed that the chiral copper complex served as a crucial factor to promote the H/D-exchange of aldimine ester **1a**. When the process of H/D-exchange was monitored over time (8 min, 16 min, 24 min, 32 min, 40 min, and 48 min), the kinetic curve of **1a**, **1a-d₁**, and **1a-d₂** gradually became steady at 32 min, which suggested that the mixed system reached an equilibrium and thus introducing dipolarophiles at this time point would be suitable for the ensuing construction of enantioenriched α-deuterated pyrrolidines *via* 1,3-dipolar cycloaddition. Accordingly, the amount of 28 equiv. of D₂O might be the compromise choice for H/D-exchange of aldimine ester, although leaving an uncertainty on whether a high level of deuterium incorporation could be achieved or not in the final pyrrolidine products, which to a great extent depends on the *in situ* formation of the deuterated azomethine ylide species *via* the selectivity of de-deuteration or de-protonation of aldimine ester **1a-d₁**.

Since the complete α-deuteration of aldimine ester **1a** into **1a-d₂** could not be reached with 28 equiv. of D₂O, the subsequent investigation commenced with the hope that a slightly more stable C–D bond would thermodynamically and kinetically favor the cleavage of the α-C–H bond rather than the α-C–D bond to form the key *N*-metallated α-deuterated azomethine ylide with a synthetically useful level of deuterium-enrichment. To explore the selectivity issue of de-deuteration or de-protonation, we started to investigate the model reaction of aldimine ester **1a** and dimethyl maleate **2a** for optimization of reaction conditions.

As shown in Table 1, aldimine ester **1a** was pre-stirred in a mixture of dichloromethane and D₂O (28 equiv.) for 30 min in the presence of Cu(I)/(S)-TF-BiphamPhos (5 mol%) and Et₃N (1 equiv.) at 5 °C. To eliminate the disfavored interference of polar deuterium solvent in the stereoselectivity of cycloaddition, 3 Å MS (200 mg) was added to remove the remaining D₂O/DHO from the system, and then dimethyl maleate **2a** was introduced at room temperature. The reaction finished smoothly to give cycloadduct *endo*-**3a** in 92% yield with an exclusive diastereoselectivity (>20 : 1 dr), excellent enantioselectivity (99% ee) and 96% deuterium incorporation (Table 1, entry 1). This excellent deuterium enrichment confirmed that the cleavage of α-C–H in **1-d₁** is kinetically more favored than that of the C–D bond even in the presence of a chiral copper catalyst. Further the control experiment revealed that removing the remaining D₂O/DHO is crucial to enhancing the reactivity and diastereoselectivity (entry 2). Using a lower amount of D₂O (7 or 14 equiv.) led to a significantly reduced deuterium-incorporation level (entries 3 and 4). Increasing the amount of D₂O to 56 equiv. could not improve the deuterium-incorporation level further (entry 5), which is fully consistent with the observation in ¹H NMR experiments (*vide supra*). When D₂O was replaced with another commonly-used deuterium reagent MeOD, a high level of deuterium-incorporation could still be achieved albeit with unsatisfactory yield and diastereoselectivity, which is probably caused by the incompatibility of the polar solvent in the catalytic asymmetric cycloaddition step (entries 6 and 7). Therefore, D₂O was chosen



Table 1 Exploration and optimization^a

Entry	Derivation from standard conditions	Yield ^b (%)	dr ^c (endo : exo)	D ^c (%)	ee ^c (%)
1	None	92	>20 : 1	96	99
2	Without 3 Å MS	82	15 : 1	96	99
3	D ₂ O (7 equiv.) instead of D ₂ O (28 equiv.)	94	>20 : 1	78	99
4	D ₂ O (14 equiv.) instead of D ₂ O (28 equiv.)	93	>20 : 1	91	99
5	D ₂ O (56 equiv.) instead of D ₂ O (28 equiv.)	92	>20 : 1	97	99
6 ^d	MeOD as solvent	85	3 : 1	96	96
7 ^d	V _{DCM} : V _{MeOD} = 10 : 1 as the solvent	80	17 : 1	95	99

^a All reactions were carried out with 0.2 mmol of **1a**, 0.3 mmol of **2a**, and 0.2 mmol of Et₃N in 2 mL of DCM and 0.1 mL of D₂O for 3–6 h, see the ESI for details. ^b Yields refer to isolated yields of deuterated products. ^c The dr value was determined by crude ¹H NMR. D refers to D-incorporation percentages based on the calculations described in the ESI. The ee value was determined by HPLC analysis. ^d Without 3 Å MS.

as the optimal deuterium-donor due to the inexpensiveness, safety and convenient operation of this material.

Substrate scope

With the optimized reaction conditions established, we turned our attention to investigating the scope and generality of the

current catalytic system with regard to aldimine esters. The representative results are shown in Table 2. A range of *para*- and *meta*-substituted aryl aldimine esters bearing electron-deficient (**1a**, **1c**, **1d**, and **1e**), electron neutral (**1f**), or electron-rich (**1g**, **1i**, and **1j**) groups on the arene ring performed well to afford the corresponding α -deuterated products **endo-3a–3j** in high yield

Table 2 Substrate scope of aldimine esters^a

Entry	R	3	Yield ^b (%)	dr ^c (endo : exo)	D ^c (%)	ee ^c (%)
1	<i>p</i> -ClC ₆ H ₄	3a	92	>20 : 1	96	99
2	<i>o</i> -ClC ₆ H ₄	3b	74	14 : 1	95	99
3	<i>m</i> -ClC ₆ H ₄	3c	67	>20 : 1	95	99
4	<i>p</i> -BrC ₆ H ₄	3d	95	17 : 1	96	99
5	<i>p</i> -FC ₆ H ₄	3e	90	13 : 1	96	99
6	Ph	3f	89	19 : 1	94	99
7	<i>p</i> -MeC ₆ H ₄	3g	88	17 : 1	96	99
8	<i>o</i> -MeC ₆ H ₄	3h	57	19 : 1	96	99
9	<i>m</i> -MeC ₆ H ₄	3i	71	13 : 1	96	97
10	<i>p</i> -MeOC ₆ H ₄	3j	90	13 : 1	94	99
11	1-Naphthyl	3k	63	13 : 1	93	99
12	2-Naphthyl	3l	56	17 : 1	95	99
13	2-Furyl	3m	66	9 : 1	96	98
14	Cyclohexyl	3n	45	>20 : 1	92	95
15 ^d	<i>p</i> -ClC ₆ H ₄	3a	95	>20 : 1	96	99

^a All reactions were carried out with 0.2 mmol of **1**, 0.3 mmol of **2**, 0.01 mmol of Cu(I)/(S)-L1, and 0.2 mmol of Et₃N in 2 mL of DCM and 0.1 mL of D₂O for 3–6 h, see the ESI for details. ^b Yields refer to isolated yields of deuterated products. ^c The dr value was determined by crude ¹H NMR. D refers to D-incorporation percentages based on the calculations described in the ESI. The ee value was determined by HPLC analysis. ^d 1.0 mmol scale.



(57–95%) with excellent stereoselectivity (13 : 1–20 : 1 dr, 97–99% ee) and uniformly high levels of (94–96%) deuterium incorporation (Table 2, entries 1, 3–7, 9 and 10). Notably, sterically hindered *ortho*-methyl and *ortho*-chloro substituted aldimine esters **1b** and **1h** were well compatible with this catalytic system, leading to the desired α -deuterated cycloadducts **3b** and **3h** in good to high yields with perfect diastereo-/enantioselectivities and excellent levels of deuterium incorporation (entries 2 and 8). Aldimine esters with fused aromatic rings (**1k** and **1l**) or heteroaryl group (**1m**) are also well tolerated

in this sequential H/D-exchange/1,3-dipolar cycloaddition process. Remarkably, the challenging and less reactive alkyl aldimine ester **1n** derived from cyclohexanecarbaldehyde is a viable substrate in this transformation, furnishing the desired α -deuterated *endo*-product (**3n**) with a high enantioselectivity (95%) and excellent deuterium incorporation (92%) with a moderate yield (45%) (entry 14). Comparable reactivity, stereoselectivity and deuterium-enrichment level were maintained when the reaction was carried out at 1.0 mmol scale (entry 15).

Table 3 Substrate scope of dipolarophiles^a

<p>[M]/L*: Ag(I)/(S)-L1 (R = <i>p</i>-ClC₆H₄) entry 1: <i>endo</i>-4a 81% yield, 94% D >20:1 dr, 95% ee</p>	<p>[M]/L*: Cu(I)/(S)-L1 (R = <i>p</i>-ClC₆H₄) entry 2: <i>endo</i>-4b 70% yield, 97% D >20:1 dr, 91% ee</p>	<p>[M]/L*: Ag(I)/(S)-L1 (R = <i>p</i>-ClC₆H₄) entry 3: <i>endo</i>-4c 88% yield, 91% D >20:1 dr, 90% ee</p>	<p>[M]/L*: Cu(I)/(S)-L1 (R = <i>p</i>-ClC₆H₄) entry 4: <i>endo</i>-4d 87% yield, 96% D >20:1 dr, 94% ee</p>	<p>[M]/L*: Cu(I)/(S)-L1 (R = <i>p</i>-ClC₆H₄) entry 5: <i>endo</i>-4e 88% yield, 94% D >20:1 dr, 90% ee</p>
<p>[M]/L*: Cu(I)/(S)-L2 (R = <i>p</i>-ClC₆H₄) entry 6: <i>exo</i>-4f 70% yield, 93% D >20:1 dr, 98% ee</p>	<p>[M]/L*: Cu(I)/(S)-L2 (R = Ph) entry 7: <i>exo</i>-4g 58% yield, 95% D >20:1 dr, 98% ee</p>	<p>[M]/L*: Cu(I)/(S)-L2 (R = Ph) entry 8: <i>exo</i>-4h 79% yield, 94% D >20:1 dr, 98% ee</p>	<p>[M]/L*: Cu(I)/(S)-L2 (R = Ph) entry 9: <i>exo</i>-4i 72% yield, 94% D >20:1 dr, 98% ee</p>	<p>[M]/L*: Cu(I)/(S)-L2 (R = <i>p</i>-ClC₆H₄) entry 10: <i>exo</i>-4j 94% yield, 93% D >20:1 dr, 99% ee</p>
<p>[M]/L*: Cu(I)/(S)-L1 entry 11: <i>endo</i>-4k, 74% yield, >20:1 dr, 99% D</p>	<p>[M]/L*: Cu(I)/(R)-L1 entry 12: <i>endo</i>-4k', 70% yield, >20:1 dr, 98% D</p>	<p>[M]/L*: Cu(I)/(S)-L2 entry 13: <i>exo</i>-4k, 53% yield, >20:1 dr, 94% D</p>	<p>[M]/L*: Cu(I)/(R)-L2 entry 14: <i>exo</i>-4k', 51% yield, >20:1 dr, 97% D</p>	

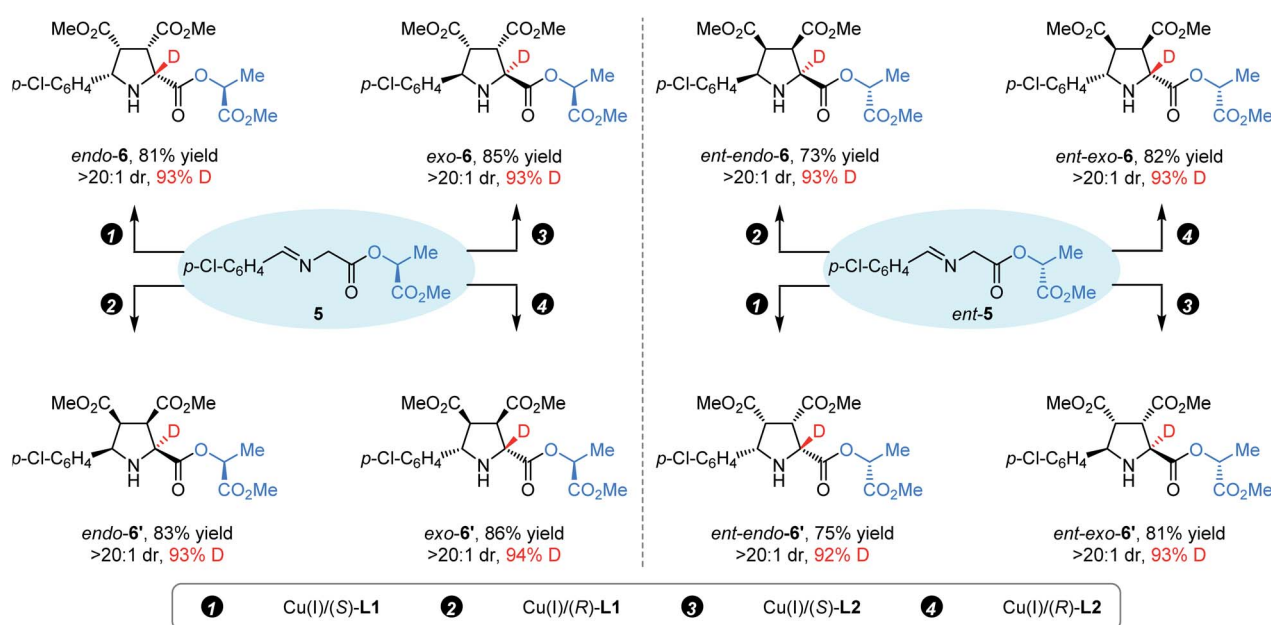
^a All reactions were carried out with 0.2 mmol of **1**, 0.3 mmol of **2**, 0.01 mmol of [M]/L, and 0.2 mmol of Et₃N in 2 mL of DCM and 0.1 mL of D₂O for 3–6 h, see the ESI for details. Yields refer to isolated yields of deuterated products. The dr value was determined by crude ¹H NMR. D refers to D-incorporation percentages based on the calculations described in the ESI. The ee value was determined by HPLC analysis.



Motivated by the excellent performance of various aldimine esters in the synthesis of α -deuterated chiral pyrrolidines, we were interested in exploring the feasibility of various electron-deficient alkenes such as dipolarophiles in this catalytic asymmetric deuteration system. As depicted in Table 3, employing (*Z*)- β -sulfonyl acrylate **2b** as the dipolarophile and aldimine ester **1a** as the ylide precursor with the AgOAc/(*S*)-**L1** complex as the chiral catalyst under otherwise identical reaction conditions,³¹ the desired cycloadduct α -deuterated *endo*-**4a** was isolated exclusively in 81% yield with 95% ee and 94% deuterium incorporation (entry 1). Subjecting *tert*-butyl acrylate **2c** to the standard reaction conditions,⁴² the corresponding α -deuterated *endo*-adduct **4b** was obtained in good yield with excellent stereoselectivity and a high level of deuterium incorporation (97%) (entry 2). Moreover, good yield and high enantioselectivity with 91% deuterium incorporation could be achieved when *N*-phenyl maleimide **2d** was employed as the reactant partner with AgOAc/(*S*)-**L1** as the metal complex (entry 3). When introducing some trisubstituted cyclic electron-deficient alkenes into the current cycloaddition reaction, highly α -deuterated *endo*-**4d** and *endo*-**4e** bearing a unique spiro quaternary carbon center were formed in good yield with excellent selectivity, respectively (entries 4 and 5). When using Cu(I)/(*S*)-DTBM-Segphos-**L2** as the chiral catalyst and dimethyl maleate **2a** as the dipolarophile,^{47,48} the corresponding α -deuterated *exo*-selective cycloadduct **4f** could be separated in 70% yield with 98% ee and 93% deuterium incorporation (entry 6). In addition, this *exo*-selective catalytic system was also highly compatible with a series of olefins bearing a single substitute such as **2g**, **2h** and **2i**, leading to formation of the desired α -deuterated cycloadducts *exo*-**4g**, *exo*-**4h** and *exo*-**4i** in good yield (58–79%) with excellent ee values (97–98%) and deuterium incorporation (94–95%) (entries 7–9). Similarly, highly α -deuterated spirocyclic *exo*-**4j** could be obtained in good yield with excellent stereoselectivity

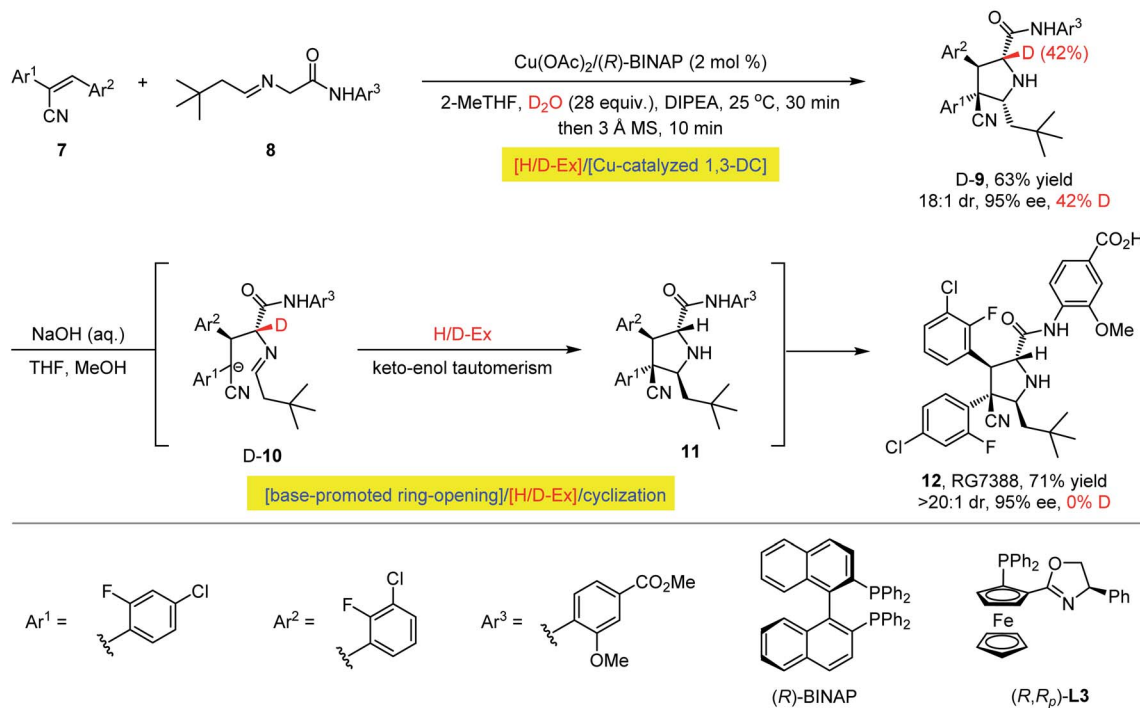
control (entry 10). To further demonstrate the scope of this methodology, we introduced a structurally complex molecular unit with biological activity into α -deuterated chiral pyrrolidines. When employing Cu(I)/(*S*)-**L1** as the metal complex, the reaction of cholesterol derived aldimine ester **1k** with **2a** under the standard reaction conditions, the corresponding *endo*-selective α -deuterated product **4k** could be separated in a good yield (74%) with an excellent diastereoselectivity (>20 : 1) and high deuterium incorporation (98%) (entry 11). Furthermore, by selecting suitable chiral ligands ((*R*)-**L1**, (*S*)-**L2**, or (*R*)-**L2**) instead of (*S*)-**L1**, controllable syntheses of the other three deuterated diastereoisomers (*endo*-**4k'**, *exo*-**4k**, and *exo*-**4k'**) could be readily accessed with satisfactory results (entries 12–14), which demonstrated that the local stereochemical information on the imine moiety of aldimine esters results in negligible effects on the H/D-exchange and asymmetric induction in the ensuing cycloaddition reaction.

Subsequently, we turned our attention to whether the above catalyst-controlled protocol for diastereodivergent synthesis of *endo*/*exo*-isomers of α -deuterated pyrrolidines could be further extended to the precise construction of up to eight deuterated *endo*/*exo*-stereoisomers. As shown in Scheme 2, the reaction of (*S*)-(-)-lactate derived aldimine ester **5** with **2a** was performed with appropriate copper(I)/chiral ligand complexes under the standard reaction conditions, and four desired α -deuterated diastereoisomers (*endo*-**6**, *endo*-**6'**, *exo*-**6**, and *endo*-**6'**) were successfully prepared in good yield (81–86%) with excellent diastereoselectivity (>20 : 1 dr) and high deuterium incorporation (93–94% D). As expected, using (*R*)-(-)-lactate derived imine ester *ent*-**5** as the starting material, the remaining four complementary α -deuterated diastereoisomers (*ent*-*endo*-**6**, *ent*-*endo*-**6'**, *ent*-*exo*-**6**, and *ent*-*endo*-**6'**) could be readily achieved with similar results *via* the same protocol.

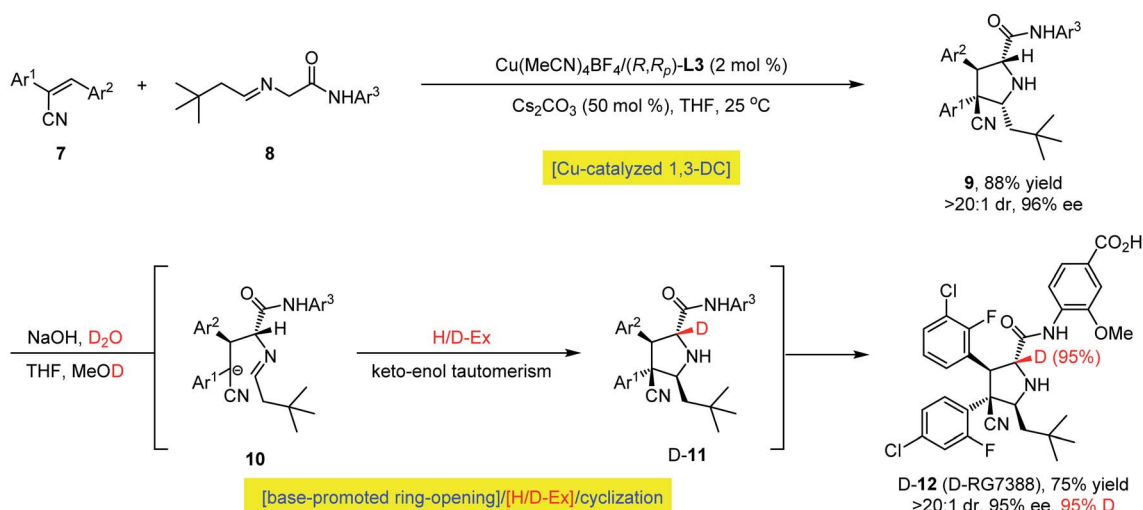


Scheme 2 Access to enantioenriched pyrrolidines *endo*-**6**, *endo*-**6'**, *exo*-**6**, and *exo*-**6'**, and the enantiomers.

a) Catalytic asymmetric synthesis of deuterated MDM2 antagonist RG7388 with the protocol of [H/D-Ex]/[Cu-catalyzed 1,3-DC]/[H/D-Ex]



b) Catalytic asymmetric synthesis of deuterated MDM2 antagonist RG7388 with the protocol of [Cu-catalyzed 1,3-DC]/[H/D-Ex]



Scheme 3 The catalytic asymmetric construction of deuterated MDM2 antagonist RG7388.

Synthetic applications

Encouraged by the above investigations on the asymmetric synthesis of enantioenriched α -deuterated pyrrolidines *via* sequential H/D-exchange/1,3-dipolar cycloaddition process, we questioned whether such protocol could be utilized for the preparation of deuterium-labelled bioactive pharmaceutical molecules. For example, MDM2 antagonist idasanutlin (RG7388), discovered by Roche, is a chiral pyrrolidine carboxamide in phase III clinical trials.⁴⁹ As shown in Scheme 3a, through integrating the H/D-exchange strategy into $\text{Cu}(\text{OAc})_2/(R)\text{-BINAP}$ -catalyzed asymmetric 1,3-dipolar cycloaddition of nitrile olefin **7** and aldimine amide **8**,⁵⁰ the corresponding α -

deuterated pyrrolidine carboxamide **D-exo-9** could be isolated in 63% yield with 18 : 1 diastereoselectivity and 95% ee albeit with unsatisfactory 42% deuterium incorporation at the α -position of ester. However, further isomerization of compound **D-exo-9** with aqueous sodium hydroxide through a base-promoted ring-opening/[H/D-Ex]/cyclization pathway⁵¹ led to idasanutlin **12** without any α -deuterium being detected albeit with retention of the configuration at the α -position of the pyrrolidine ring, and the key keto-enol tautomerization resulted in the complete loss of deuterium in a regular protic solvent. In consideration of the correlation between the deuteration of unlabeled compounds in deuterium solvents and the reverse de-deuteration of labelled



compounds in common solvents⁵² and the previous ¹H NMR experimental results of the α -hydrogen atom of aldimine esters could be partially deuterated with D₂O in the presence of weak organic base Et₃N (*vide supra*, Fig. 2), we reasoned that using a stronger inorganic base (aqueous sodium hydroxide), it would be possible to install a deuterium atom onto the α -position of idasanutlin with a synthetically useful deuteration level *via* a reversed 1,3-DC/[H/D-Ex] protocol. As shown in Scheme 3b, Cu(I)/(R,R)-L3-catalyzed 1,3-dipolar cycloaddition between nitrile olefin **7** and aldimine amide **8** proceeded smoothly in THF to provide the regular compound *exo*-**9** in 88% yield with an exclusive diastereoselectivity (>20 : 1 dr) and 96% ee.⁴⁷ The ensuing isomerization was successfully carried out in a mixed solution of NaOH/D₂O (10 M), leading to the α -deuterated idasanutlin D-**12** (D-RG7388) in 75% yield with a high level of deuteration incorporation (95% D) and excellent stereoselectivity (>20 : 1 dr, 95% ee).

Conclusions

In summary, a wide range of enantioenriched pyrrolidine derivatives with a high level of deuteration incorporation have been efficiently synthesized for the first time *via* the strategy of merging H/D exchange with the transition-metal catalyzed 1,3-dipolar cycloaddition reaction. Directly converting glycine-derived aldimine esters into the deuterated counterparts with D₂O by virtue of Cu(I)-catalyzed H/D-exchange and subsequent thermodynamically/kinetically favored cleavage of the α -C-H bond rather than the α -C-D bond are crucial to generate the key *N*-metallated α -deuterated azomethine ylide species, which enables the success of α -deuterated chiral pyrrolidine synthesis with a high level of deuterium incorporation. The cost-effective and operationally simple protocol not only precisely installs a unique deuterium-containing stereogenic center but also makes contributions to the development of deuterated heterocycle chemistry. The application of such a strategy was further demonstrated through a catalytic asymmetric synthesis of deuterium-labelled MDM2 antagonist idasanutlin (RG7388) *via* a reversed 1,3-DC/[H/D-exchange] protocol. We anticipate that the current method will be helpful in the construction of deuterated chiral heterocycles to enable new drug discovery.

Data availability

All experimental and characterization data in this manuscript are available in the ESI.†

Author contributions

C.-J. W. conceived and designed the research. X. C. and X. C. performed the research. C. J. W. and X. C. co-wrote the paper. All the authors analysed the data, discussed the results, and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 T. Pirali, M. Serafini, S. Cargnin and A. A. Genazzani, *J. Med. Chem.*, 2019, **62**, 5276–5297.
- 2 J. Atzrodt, V. Derdau, W. J. Kerr and M. Reid, *Angew. Chem., Int. Ed.*, 2018, **57**, 1758–1784.
- 3 T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595–3611.
- 4 S. Kopf, F. Bourriquet, W. Li, H. Neumann, K. Junge and M. Beller, *Chem. Rev.*, 2022, DOI: 10.1021/acs.chemrev.1c00795.
- 5 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066–3072.
- 6 K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713–743.
- 7 E. Stokvis, H. Rosing and J. H. Beijnen, *Rapid Commun. Mass Spectrom.*, 2005, **19**, 401–407.
- 8 V. Jacques, A. W. Czarnik, T. M. Judge, L. H. T. Van der Ploeg and S. H. DeWitt, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, E1471–E1479.
- 9 G. W. Muller, P. H. Schafer, H.-W. Man, L.-H. Zhang, A. Gandhi and R. Chopra, *US Pat.*, 20120230983A1, 2012.
- 10 F. Maltais, Y. C. Jung, M. Chen, J. Tanoury, R. B. Perni, N. Mani, L. Laitinen, H. Huang, S. Liao, H. Gao, H. Tsao, E. Block, C. Ma, R. S. Shawgo, C. Town, C. L. Brummel, D. Howe, S. Pazhanisamy, S. Raybuck, M. Namchuk and Y. L. Bennani, *J. Med. Chem.*, 2009, **52**, 7993–8001.
- 11 P. K. Bhadra, A. Hassanzadeh, B. Arsic, D. G. Allison, G. A. Morris and J. Barber, *Org. Biomol. Chem.*, 2016, **14**, 6289–6296.
- 12 S. Dewitt, V. Jacques and L. H. T. Van der Ploeg, 2016153948A1, PTC Int., 2016.
- 13 A. Katsnelson, *Nat. Med.*, 2013, **19**, 656.
- 14 J. Helfenbein, C. Lartigue, E. Noirault, E. Azim, J. Legaillard, M. J. Galmier and J. C. Madelmont, *J. Med. Chem.*, 2002, **45**, 5806–5808.
- 15 J. Bigeleisen, *Science*, 1965, **147**, 463–471.
- 16 J. Atzrodt, V. Derdau, W. J. Kerr and M. Reid, *Angew. Chem., Int. Ed.*, 2018, **57**, 3022–3047.
- 17 J. Atzrodt, V. Derdau, T. Fey and J. Zimmermann, *Angew. Chem., Int. Ed.*, 2007, **46**, 7744–7765.
- 18 P. Ji, Y. Zhang, Y. Dong, H. Huang, Y. Wei and W. Wang, *Org. Lett.*, 2020, **22**, 1557–1562.
- 19 W. N. Palmer and P. J. Chirik, *ACS Catal.*, 2017, **7**, 5674–5678.
- 20 L. V. A. Hale and N. K. Szymczak, *J. Am. Chem. Soc.*, 2016, **138**, 13489–13492.
- 21 C. Taglang, L. M. Martínez-Prieto, I. del Rosal, L. Maron, R. Poteau, K. Philippot, B. Chaudret, S. Perato, A. Sam Lone, C. Puente, C. Dugave, B. Rousseau and G. Pieters, *Angew. Chem., Int. Ed.*, 2015, **54**, 10474–10477.



- 22 J. S. Rowbotham, H. A. Reeve and K. A. Vincent, *ACS Catal.*, 2021, **11**, 2596–2604.
- 23 S. Guo, X. Wang and J. S. Zhou, *Org. Lett.*, 2020, **22**, 1204–1207.
- 24 T. Sakamoto, K. Mori and T. Akiyama, *Org. Lett.*, 2012, **14**, 3312–3315.
- 25 E. J. Corey and J. O. Link, *Tetrahedron Lett.*, 1989, **30**, 6275–6278.
- 26 H. Mizutani, R. Kawanishi and K. Shibatomi, *Chem. Commun.*, 2021, **57**, 6676–6679.
- 27 T. Shao, Y. Li, N. Ma, C. Li, G. Chai, X. Zhao, B. Qiao and Z. Jiang, *iScience*, 2019, **16**, 410–419.
- 28 K. Moozeh, S. M. So and J. Chin, *Angew. Chem., Int. Ed.*, 2015, **54**, 9381–9385.
- 29 Y. Zhao, X. Lim, Y. Pan, L. Zong, W. Feng, C.-H. Tan and K.-W. Huang, *Chem. Commun.*, 2012, **48**, 5479–5481.
- 30 J.-S. Oh, K. I. Kim and C. E. Song, *Org. Biomol. Chem.*, 2011, **9**, 7983–7985.
- 31 L. Wei, X. Chang and C.-J. Wang, *Acc. Chem. Res.*, 2020, **53**, 1084–1100.
- 32 X. Fang and C.-J. Wang, *Org. Biomol. Chem.*, 2018, **16**, 2591–2601.
- 33 J. Adrio and J. C. Carretero, *Chem. Commun.*, 2019, **55**, 11979–11991.
- 34 T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366–5412.
- 35 J. M. Longmire, B. Wang and X. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13400–13401.
- 36 M. Kuhnert, A. Blum, H. Steuber and W. E. Diederich, *J. Med. Chem.*, 2015, **58**, 4845–4850.
- 37 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3479.
- 38 Y. Zhao, A. Aguilar, D. Bernard and S. Wang, *J. Med. Chem.*, 2015, **58**, 1038–1052.
- 39 P. Beak, S. T. Kerrick, S. Wu and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231–3239.
- 40 A. Michelotti, F. Rodrigues and M. Roche, *Org. Process Res. Dev.*, 2017, **21**, 1741–1744.
- 41 X. Chang, Y. Yang, C. Shen, K.-S. Xue, Z.-F. Wang, H. Cong, H.-Y. Tao, L. W. Chung and C.-J. Wang, *J. Am. Chem. Soc.*, 2021, **143**, 3519–3535.
- 42 C.-J. Wang, G. Liang, Z.-Y. Xue and F. Gao, *J. Am. Chem. Soc.*, 2008, **130**, 17250–17251.
- 43 P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P. K. Rajanna, H. Bhutani, A. T. Paul and R. Kumar, *J. Med. Chem.*, 2021, **64**, 2339–2381.
- 44 B. Lygo and L. D. Humphreys, *Tetrahedron Lett.*, 2002, **43**, 6677–6679.
- 45 T. Yamada, M. Kuwata, R. Takakura, Y. Monguchi, H. Sajiki and Y. Sawama, *Adv. Synth. Catal.*, 2018, **360**, 637–641.
- 46 H. Geng, X. Chen, J. Gui, Y. Zhang, Z. Shen, P. Qian, J. Chen, S. Zhang and W. Wang, *Nat. Catal.*, 2019, **2**, 1071–1077.
- 47 W. Gao, X. Zhang and M. Raghunath, *Org. Lett.*, 2005, **7**, 4241–4244.
- 48 G. S. Caleffi, O. Larrañaga, M. Ferrándiz-Saperas, P. R. R. Costa, C. Nájera, A. de Cózar, F. P. Cossío and J. M. Sansano, *J. Org. Chem.*, 2019, **84**, 10593–10605.
- 49 Q. Ding, Z. Zhang, J.-J. Liu, N. Jiang, J. Zhang, T. M. Ross, X.-J. Chu, D. Bartkovitz, F. Podlaski, C. Janson, C. Tovar, Z. M. Filipovic, B. Higgins, K. Glenn, K. Packman, L. T. Vassilev and B. Graves, *J. Med. Chem.*, 2013, **56**, 5979–5983.
- 50 L. Shu, C. Gu, D. Fishlock and Z. Li, *Org. Process Res. Dev.*, 2016, **20**, 2050–2056.
- 51 G. Rimmeler, A. Alker, M. Bosco, R. Diodone, D. Fishlock, S. Hildbrand, B. Kuhn, C. Moessner, C. Peters, P. D. Rege and M. Schantz, *Org. Process Res. Dev.*, 2016, **20**, 2057–2066.
- 52 A. Di Giuseppe, R. Castarlenas and L. A. Oro, *C. R. Chim.*, 2015, **18**, 713–741.

