ChemPubSoc Europe

DOI: 10.1002/chem.201602900

CHEMISTRY
A European Journal
Full Paper

Diketone Site Selectivity

Beyond Chemoselectivity: Catalytic Site-Selective Aldolization of Diketones and Exploitation for Enantioselective Alzheimer's Drug Candidate Synthesis

Thomas C. Nugent,* Foad Tehrani Najafian, Hussein Ali El Damrany Hussein, and Ishtiaq Hussain[a]

Abstract: Site selectivity, differentiating instances of the same functional group type on one substrate, represents a forward-looking theme within chemistry: reduced dependence on protection/deprotection protocols for increased overall yield and step-efficiency. Despite these potential benefits and the expanded tactical advantages afforded to synthetic design, site selectivity remains elusive and especially so for ketone-based substrates. Herein, site-selective intermolecular mono-aldolization has been demonstrated for an array of prochiral 4-keto-substituted cyclohexanones with concomitant regio-, diastereo-, and enantiocontrol. Importantly, the aldol products allow rapid access to molecularly complex ketolactones or keto-1,3-diols, respectively containing three and four stereogenic centers. The reaction conditions are of immediate practical value and general enough to be applicable to other reaction types. These findings are applied in the first enantioselective, formal, synthesis of a leading Alzheimer's research drug, a γ-secretase modulator (GSM), in the highest known yield.

Introduction

Differentiation of the same functional group type on one molecule is a challenge of site-selective transformations,[1] a subcategory of regioselectivity. Mild reagents sometimes achieve site selectivity when recognizable steric or electronic dissimilarities prevail, but when subtle differences exist the product outcomes are nonselective. The latter issue is the focus of this study, and catalyst design can be pivotal in addressing this challenge. The most successful applications of site selectivity have been demonstrated for polyol substrates, and elegant natural product examples have been demonstrated in the name of expedited drug discovery.[2,3] In parallel, a smaller subset of polyols, for example, *meso*-diols, require desymmetrization to differentiate their alcohol moieties.[4,5]

In contrast to these achievements with polyol substrates, little is known about controlling the reaction outcome at one of two electronically disconnected ketone functional groups within a 1,*n*-diketone where $n \geq 4$. These substrates are the focus of this study and, to our knowledge, only four systematic studies have detailed site selectivity or desymmetrization with high enantioselectivity (Figure 1). It is informative that half of those investigations resulted in tactical advantages that permitted the shortest known syntheses of two natural products

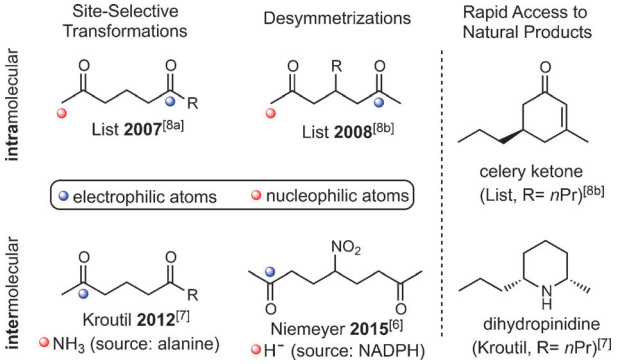


Figure 1. Left: diketone starting materials of prior site selectivity or desymmetrization studies; right: natural product applications. Blue-labeled atoms are electrophilic and red-labeled atoms are nucleophilic.

(Figure 1, right panel). Two of those four studies, by the groups of Niemeyer and Kroutil, employed enzymes and intimated how to reduce[6] or reductively aminate[7] one carbonyl unit, specifically a methyl ketone. The remaining two studies, both by List and co-workers,[8] were chemical based and demonstrated how to perform *intramolecular* reactions, again with methyl ketones (Figure 1). For all four studies, excellent selectivities were reported. We are additionally aware of a single example of double *intermolecular* site-selective aldolization of a methyl ketone within a diketone (not shown).[9] Finally, it is important to note the *intramolecular* aldol studies of the Hajos–Parrish–Eder–Sauer–Wiechert triketones. These triketones (not shown) and analogs thereof have been studied and

[a] *Prof. T. C. Nugent, F. T. Najafian, H. A. E. D. Hussein, I. Hussain*
Department of Life Sciences and Chemistry, Jacobs University Bremen
Campus Ring 1, 28759 Bremen (Germany)
E-mail: t.nugent@jacobs-university.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201602900.

reviewed elsewhere,[10–13] and all conclusions made herein take those findings into account.

General guidance on how to broaden or improve ketone site selectivity is not apparent from the small number of studies (Figure 1) within this emerging field; and catalyst loadings can be prohibitively high. Furthermore, many challenges remain open to investigation; for example, whether methyl ketones can be preserved (remain unreacted) while another type of ketone carbonyl undergoes a transformation. A useful entry point into that question is Stork's 1963 observation that stoichiometric pyrrolidine enamine formation is more rapid for cyclohexanone than for acyclic ketones.[14] Those results are in general agreement with the last fifteen years of modern enamine-based organocatalysis observations.[10,11,13,15] For example, List et al. demonstrated rather early that L-proline (**1**; Figure 2) produced the aldol products of cyclohexanone faster than those of acetone.[16] However, these trends can also be interrupted. For example, it has been repeatedly shown that 2-butanone and cyclohexanone react with *p*-nitrobenzaldehyde by way of L-proline[17] or various prolinamide[18] catalysts, under the same reaction conditions and times, to produce remarkably similar aldol product yields of each. Nevertheless, when starting materials are not used in excess, clearer reactivity trends can sometimes be noted for particular amine catalysts. For example, Hayashi's aldol studies of *tert*-butyldiphenylsilyloxy (TBDPSO) 4-hydroxyproline catalyst **2** (Figure 2) revealed a large difference in reactivity for 2-butanone and cyclohexanone.[19] In summary, despite long-held knowledge of cyclohexanone enamine formation and reactivity trends, it is remarkable that those differences have never been demonstrated within a multiketonic substrate, let alone exploited for synthetic advantage. This manuscript details the first inroads toward that goal.

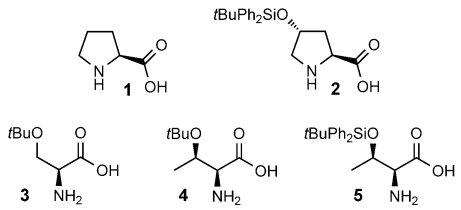


Figure 2. Catalysts examined during this study.

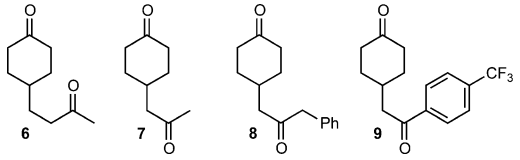


Figure 3. Diketones investigated.

Results and Discussion

We speculated that 4-keto-substituted cyclohexanones **6**–**9** (Figure 3) could serve as prototypes to establish broader knowledge in this area and envisioned that chiral amine catalysts would permit high aldol site selectivity. This would be possible if the intermediary enamines would have dramatically different enamine equilibria with the available, and competing, ketone carbonyl moieties.[20] Over the course of this study we show that this was possible and demonstrated: i) the first reactions in which unhindered methyl ketones remain unreacted, ii) the first comprehensive chemical study to show that *intermolecular* ketone site selectivity is possible, and iii) the beneficial application of this procedure in the highest yielding synthesis reported to date of a recently described frontline Alzheimer's drug candidate (see Scheme 2).[21,22,23]

Diketone **6** is a compelling starting point because it merges 2-butanone and cyclohexanone into one diketone substrate. Its reaction with *p*-nitrobenzaldehyde under TBDPSO-4-hydroxyproline (**2**) catalysis can yield up to twenty-one possible products (Figure 4, left panel). However, only two products of type **D**, specifically from cyclohexanone carbonyl attack, were noted: **11a** (major) and **12a** (minor; Figure 4, right panel). Two regioisomeric intermolecular aldol products of the methyl

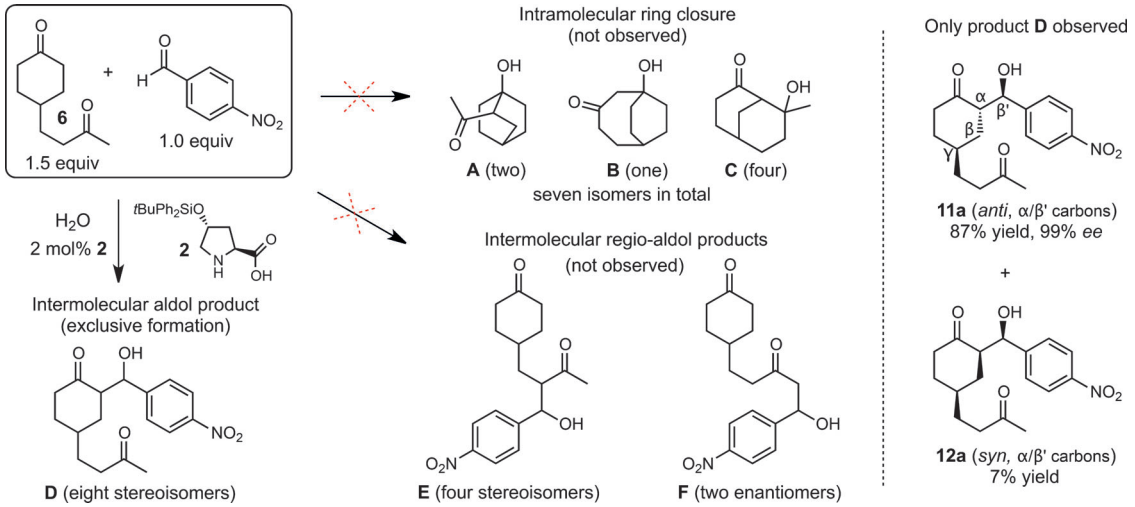
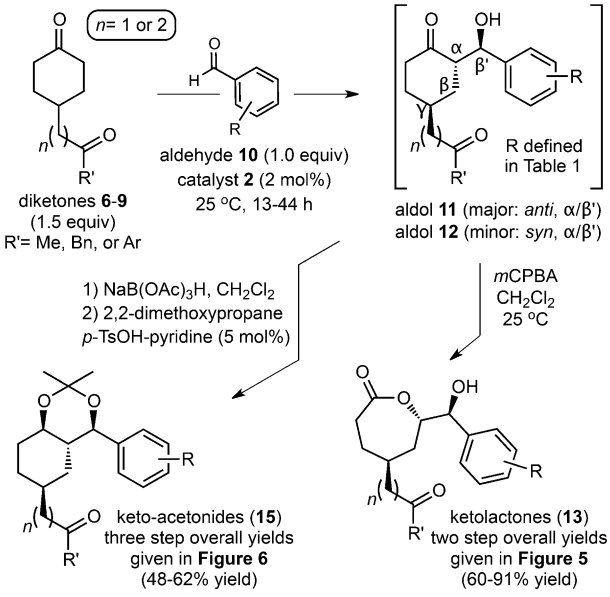


Figure 4. Left: twenty-one possible first generation products; right: only two stereoisomers of product type **D** are detected (**11a** and **12a**).

ketone are also possible: **E** and **F** (Figure 4, left panel), but no evidence of their formation was detected. Although intramolecular aldol cyclization may occur (e.g., product types **A** and **C** are Baldwin favored),[24,25] control experiments, without the aldehyde, ruled out this possibility by returning only the starting diketone (**6**). In that light, it is interesting to note that a closely related compound does undergo intramolecular cyclization in the presence of catalyst **2**, namely, the corresponding aldehydic cyclohexanone (not shown), which replaces the methyl ketone of **6** with an aldehyde moiety.[26] In conclusion, the formation of **11 a** (87% yield, 99% *ee*) represents a highly site-selective differentiation of diketone **6** with concomitant diastereo- and enantiocontrol.

To preserve the α-keto labile stereogenic centers of aldol products **11**,[27] they were worked up by organic solvent extraction from water and dried under high vacuum. Their diastereomeric ratios were assessed by ^{1}H NMR spectroscopy (Table 1) and the crude aldol products oxidized or reduced to respectively give previously unknown, but stable and fully characterizable, ketolactones (**13**, three stereogenic centers; Scheme 1) or keto-1,3-diols (**14**, not shown), which were identified as their keto-acetonide analogues (**15**, four stereogenic centers; Scheme 1). Products **13** and **15** were isolated after column chromatography as single diastereoisomers and the overall yields of each diastereoisomer, calculated from the aldehyde limiting reagent used for the aldol reactions with diketones (**6**-**9**), were good to excellent, given that these yields respectively reflect two or three reaction steps (Scheme 1 and Figures 5 and 6). Conversion of aldol products **11** into **13** or **15** constituted a second, albeit predictable, level of site selectivity based, respectively, on well-established Baeyer–Villiger migratory aptitudes[28] and the known proclivity of $NaB(OAc)_3H$ to chemoselectively reduce β-hydroxyketones selectively over ketones.[29,30,31]



Scheme 1. Ketone site selectivity and overview of: aldol, ketolactone, and keto-acetonide products.

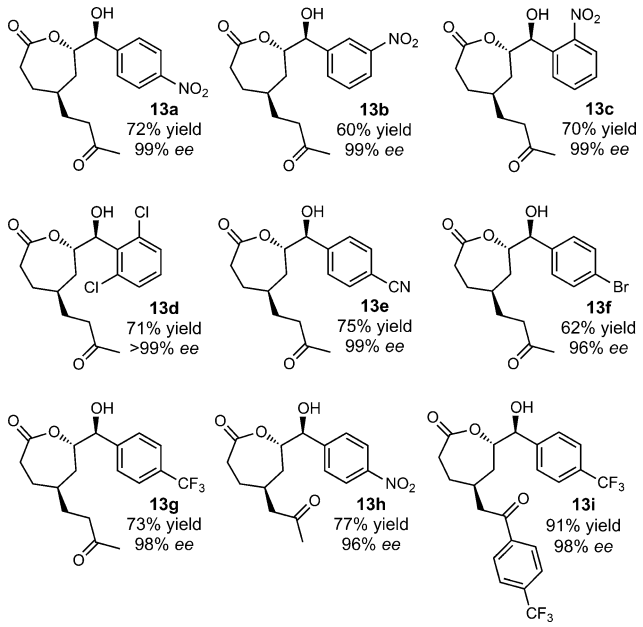


Figure 5. Ketolactone products (Scheme 1) with two-step overall yields from the corresponding aldehyde limiting reagent reacted with diketones (**6**, **7**, or **9**). Each product represents a single diastereomerically pure compound after column chromatography.

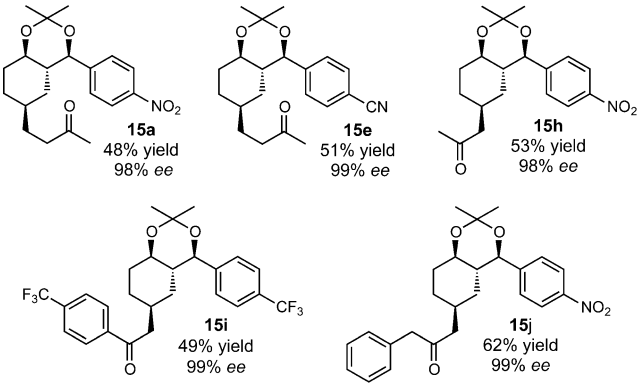


Figure 6. Keto-acetonide products (Scheme 1) with three-step overall yields from the corresponding aldehyde limiting reagent reacted with diketones (**6**–**9**). Each product represents a single diastereomerically pure compound after column chromatography.

Screening and catalyst optimization of the aldol reactions were guided by the fact that the *O*-protected serine,[32] threonine,[33] and 4-hydroxyproline[34] catalyst frameworks had been previously reported for the aldol desymmetrization of 4-methylcyclohexanone.[35] The reactions of catalysts **3**–**5** (5.0 mol%; Figure 2) with diketone **6** and *p*-nitrobenzaldehyde were incomplete, except for **5**, and resulted in mediocre diastereoselectivities (2:1 to 3.5:1) at the remote γ stereogenic center. To our knowledge, a silyl protected 4-hydroxyproline,[34a] such as TBDPSO-4-hydroxyproline **2** (Figure 2), has never been examined as a catalyst for the desymmetrization of 4-substituted cyclohexanones. It was thus gratifying to find that catalyst **2** provided aldol product **11 a** with greater than 24:1 diastereoselectivity at the remote stereogenic center. This high remote

Table 1. Reaction conditions and diastereomeric ratios (**11**/**12**) for the aldol reaction depicted in Scheme 1.[a]

Entry	Diketone	R	t [h][b]	Aldol products **11**/**12**	d.r.[c]
1	**6**	4-NO_2	30	**11a**/**12a**	12:1
2[d]	**6**	4-NO_2	80	**11a**/**12a**	6:1
3[e]	**6**	3-NO_2	30	**11b**/**12b**	19:1
4	**6**	2-NO_2	38	**11c**/**12c**	>24:1
5	**6**	2,6-Cl_2	30	**11d**/**12d**	>24:1
6	**6**	4-CN	36	**11e**/**12e**	13:1
7[e]	**6**	4-Br	28	**11f**/**12f**	3.3:1
8	**6**	4-CF_3	30	**11g**/**12g**	10:1
9	**7**	4-NO_2	34	**11h**/**12h**	17:1
10[f,g,h]	**8**	4-NO_2	13	**11j**/**12j**	6.3:1
11[f,g,i]	**8**	4-NO_2	23	**11j**/**12j**	8.2:1
12[h,j]	**9**	4-CF_3	44	**11i**/**12i**	>24:1

[a] Conditions (unless otherwise stated): aldehyde (0.50 or 0.75 mmol), diketone (1.5 equiv), water (3.0 equiv), catalyst **2** (2.0 mol%), 25 °C; aldol products are stereochemically labile and further reacted without purification, no yield data; [b] t corresponds to aldehyde consumption (^{1}H NMR spectroscopy) of 95±2%; [c] from ^{1}H NMR spectra of crude *anti*-**11**/*syn*-**12** (α and β' carbons); [d] 50 mol% L-proline used as catalyst; [e] t corresponds to aldehyde consumption (^{1}H NMR spectroscopy) of 91±2%; [f] T=35 °C; [g] 8.0 equivalents of H_2O; [h] catalyst **2** (4.0 mol%); [i] catalyst **2** (2.0 mol%) added at t=0 and 9 h; total catalyst loading=4 mol%; [j] diketone **9** is the limiting reagent; aldehyde (2.0 equiv), H_2O (4.5 equiv), 25 °C.

center diastereoselectivity was noted for all aldol products formed in this study. The use of L-proline provided the same high remote center diastereoselectivity, but required a 50 mol% catalyst loading and an 80 h reaction time (Table 1, entry 2). The result with L-proline offers the possibility of improvement by the ball-milling technique reported by Bolm and co-workers,[35a] although this method was not pursued here. Generation of this remote stereogenic center in high diastereomeric ratio was the pivotal stereochemical element allowing access to the later discussed Alzheimer's research drugs (see below, Scheme 2).

Further investigation of this system demonstrated that aromatic aldehydes, present as the limiting reagents and under chiral amine catalysis (2.0 mol% of **2**), could site selectively desymmetrize a diverse set of achiral 4-keto-substituted cyclohexanones **6**–**8** (1.5 equiv). In doing so, cyclohexanone-substituted aldol products **11** and **12** were produced (Scheme 1, Table 1), mostly in diastereomeric ratios (*anti*-**11**/*syn*-**12**, α and β' carbons) of greater than 10:1 and with high enantioselectivities (96–99% *ee*), as observed in the final products **13** and **15**. Details of the reactions involving diketone **9** are given in the discussion of the Alzheimer's drug synthesis.

Regarding the structural breadth of the aldehyde electrophiles, steric effects can restrict the addition of *ortho*-substituted benzaldehydes but here they are well tolerated, as shown by the addition of 2-nitrobenzaldehyde and 2,6-dichlorobenzaldehyde, respectively forming ketolactones **13c** and **13d** (Figure 5). Finally, from an electronic point of view, high-yielding substrates are those that incorporate aromatic substituents with either inductive or resonance-based electron-withdrawing effects. Benzaldehyde itself provided a low aldol yield under extended reaction times of four days, even with elevated catalyst loadings (10 mol%). Trials examining this aldehyde were not further pursued.

Of importance, diketone substrates **7** and **9** may be more prone than diketone **6** to undergo intramolecular aldol reactions because each of them has three Baldwin favored intramolecular aldol ring closure possibilities (as opposed to two for diketone **6**), and furthermore, **9** contains a more electrophilic *p*-trifluoromethyl phenylketone carbonyl moiety as compared to a methyl ketone. Despite these increased alternative possibilities, both **7** and **9** maintain high selectivity for the cyclohexanone carbonyl (Table 1, entries 9 and 12; Figure 5, **13h** and **13i**; Figure 6, **15h** and **15i**). Finally, we studied benzyl diketone **8** because a related proline catalyst was shown to have a very similar propensity for enamine formation with either cyclohexanone or methyl benzyl ketone.[20] Again, the cyclohexanone carbonyl was the only site of attack (see Table 1, entries 10 and 11; Figure 6, keto-acetonide **15j**), presumably due to its lack of steric congestion as compared to the enamine of the benzyl ketone moiety. Attempts to convert the aldol product **11j** of benzyl diketone **8** into a ketolactone resulted in low yields due to competitive, albeit nonselective, Baeyer–Villiger migration of the benzylic carbonyl substituent versus the desired secondary carbon carbonyl substituent.

X-ray crystallographic analysis and circular dichroism (CD) spectroscopy (see the Supporting Information, section 5) of keto-acetonide **15i** provided the relative and absolute stereochemistry for that product and, by extension, for all depicted aldol products (Figures 5 and 6). The transition state depicted in Figure 7 shows a likely scenario for the formation of aldol **11i** through the reaction of diketone **9** with *p*-trifluoromethyl benzaldehyde, which in turn was elaborated into keto-acetonide **15i**.

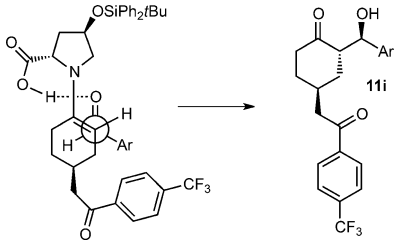
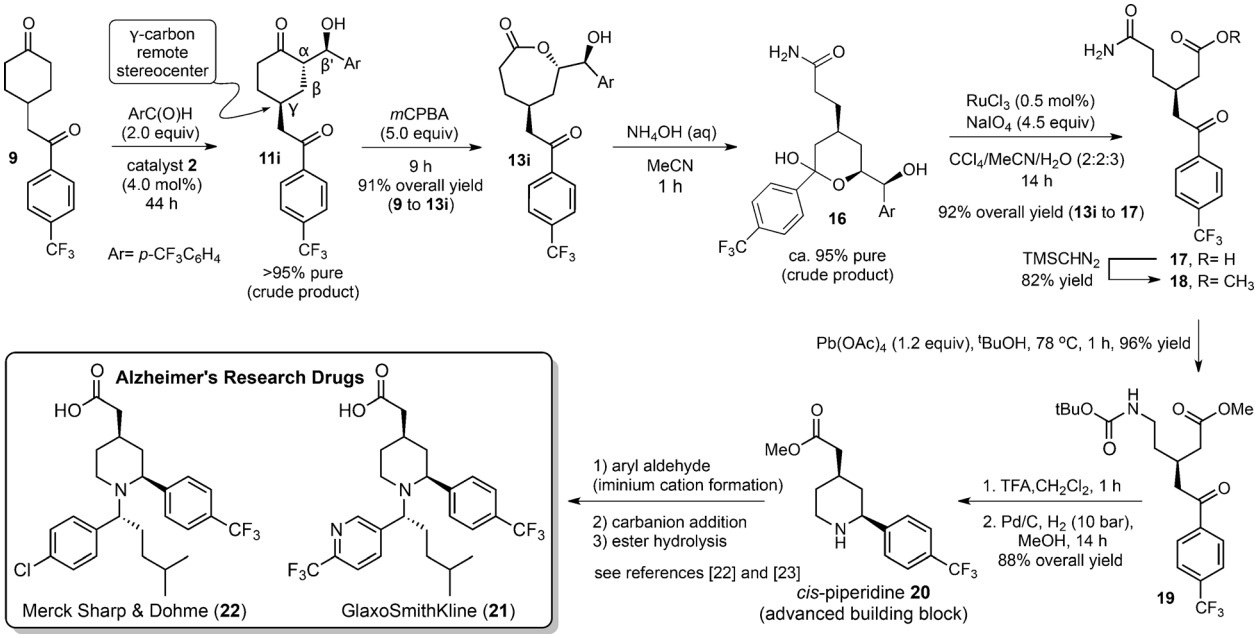


Figure 7. Proposed transition state for aldol **11i**.

In brief summary, most of the aldol reactions were performed with diketone **6** to unequivocally demonstrate that a non-hindered methyl ketone repeatedly showed no reactivity. It is clear that methyl-ketones act as if they are protected under these mild reaction conditions. These results complement the earlier findings, all of which required the reaction of a methyl ketone within diketone substrates (Figure 1).

Early onset Alzheimer's disease is marked by proteolysis events initiated by β-secretase but refined multiple times by γ-secretase.[36] The most frequent outcome is amyloid beta (Aβ) peptide formation in the range of 37–43 amino acid residues.[37] In the Alzheimer's patient, this manifests itself as neurotoxic Aβ_{42} peptide brain deposition, otherwise known, in one



Scheme 2. The first enantioselective synthesis of piperidine **20** and formal synthesis of Alzheimer's drug candidates **21** and **22**.

typical form, as extracellular senile plaque. At present, no drugs are known for the treatment of Alzheimer's disease, but leading drugs currently under investigation are γ-secretase modulators (GSMs).[21] GSMs were explicitly developed for reducing $A\beta_{42}$ peptide formation, and include the investigational drug examples synthesized by GlaxoSmithKline (**21**)[23,38] and Merck, Sharp & Dohme (**22;** Scheme 2).[22] Both companies leveraged one advanced enantiopure piperidine building block (**20**) to produce well over 100 drug candidates.[22,23,39] Of those, the most often and very recently cited representative, with potent $A\beta_{42}$ peptide-lowering effects, is the piperidine-based amino acid **22**.[21,37,40,41]

All syntheses of these Alzheimer's drugs proceed through enantiopure *cis*-piperidine **20**. Our route to **20** was envisioned through lactone **13 i** because we could repeatedly obtain exceptionally high overall yield (91%) and enantioselectivity (98% *ee*) from diketone **9** and *p*-trifluoromethyl benzaldehyde (Scheme 2). The reaction is robust, regardless of the scale of the reaction, which varied from 1 to 15 mmol. To obtain these results, we modified our general procedure as follows. Diketone **9** became the limiting reagent (1.0 equiv) in the presence of excess *p*-trifluoromethyl benzaldehyde (2.0 equiv) and water (4.5 equiv). After 44 h, the ring-substituted aldol products **11 i** and **12 i** formed in an *anti*-(α,β′)/*syn*-(α,β′) ratio of greater than 24:1 (Scheme 2; **12 i** not shown). Extractive workup gave **11 i**/**12 i** in high crude yield and purity (≥95%). This material could be used without further purification in the next reaction step.

Transformation of aldol **11 i** into lactone **13 i** required the cyclic ketone's secondary-carbon substituent to undergo Baeyer–Villiger migration while the acyclic ketone's aromatic substituent remained unreacted. These two types of substituents have similar migratory aptitudes, but we were confident that this aromatic ring would not migrate because Baeyer–Villiger rearrangements with strongly electron-withdrawing *para*-substituents on the aromatic ring, to our knowledge, have no published precedent when using *meta*-chloroperbenzoic acid (*m*CPBA). Our results bear out that conclusion, with a 91% overall yield of lactone **13 i** from diketone **9**, as one diastereomerically pure compound after column chromatography (Scheme 2). This is an uncommon demonstration of an electronic effect dictating Baeyer–Villiger migratory aptitude.[28]

Ammonolysis of **13 i** quantitatively provided the ring-opened primary amide, whose concomitantly liberated diol preferred to collapse onto the aromatic ketone resulting in the six-membered lactol **16** (Scheme 2). Lactol **16** resisted high level purification, which may reflect diastereomeric lactol interconversions (see the Supporting Information, section 6). This prompted us to use this nearly pure crude product as such. The next reaction, a catalytic ruthenium (0.50 mol%)-based oxidative cleavage, occurred under mildly acidic aqueous biphasic conditions. These conditions advantageously promoted in situ lactol hydrolysis, temporarily freeing the vicinal diol whose oxidative cleavage produced an aldehyde that was readily oxidized to the desired carboxylic acid **17** in the presence of catalytic perruthenate. Thus, in one pot, lactol **16** was converted into carboxylic acid **17**. The isolated overall yield of **17** from lactone **13 i** was 92%. Treatment of **17** with ethereal trimethylsilyl diazomethane gave the methyl ester **18** in 82% yield (Scheme 2).

We initially sought to convert methyl ester **18** into piperidine **20** by Hofmann rearrangement, but otherwise reliable modern reagents for doing so, $PhI(CF_3CO_2)_2$[42] or $PhI(OAc)_2$,[43] provided intractable product mixtures. This is perhaps unsurprising, given the number, type, and proximity of the present spectator functional groups. By contrast, the combination of 1.2 equivalents of lead tetraacetate in near-boiling *tert*-butanol proved efficient for isocyanate formation,[44] affording the *tert*-butoxycarbonyl (boc)-protected amine **19** in high yield after in

situ solvent trapping. Deprotection of carbamate **19** proceeded satisfactorily in a one-spot to one-spot transformation (monitored by TLC) with trifluoroacetic acid (25 equiv). Hydrogenation (2.0 mol% Pd/C, 10 bar H_2) exclusively from the less hindered face of the resulting crude cyclic imine (not shown) provided the desired *cis*-piperidine **20** at the expense of the undesired *trans* diastereoisomer. This synthesis constitutes the first enantioselective synthesis of *cis*-piperidine **20** and by extension, the first (formal) enantioselective synthesis of γ-secretase modulators **21** and **22** (Scheme 2). The latter is sometimes referred to in the neuroscience literature as GSM-1.[40]

The present synthesis constitutes a seven-step high-yielding transformation of diketone **9** into *cis*-piperidine **20**, occurring in an overall yield of 58%. A 36% overall yield of *cis*-piperidine **20** is noted when starting from 1,1-ethylenedioxy-4-cyclohexanone, the commercial starting material required for the synthesis of diketone **9** (see the Supporting Information, section 2). This overall yield improves the best previously reported synthesis of *cis*-piperidine **20**,[22,23] which required resolution with L-(+)-mandelic acid and gave 25% overall yield.[23]

Conclusion

In summary, mild amine catalysis enabled the regio-, diastereo-, and enantioselective differentiation of a diverse set of cyclohexanone-based diketones (**6**–**9**) during aldol reactions. The present method has accordingly established new chemical territory for further exploration by offering previously unrealized site selectivity for diketone substrates. Importantly, the aldol products reported herein allow fast entry to high-density chiral compounds including ketolactones (**13**) and keto-acetonides (**15**) under practical reaction conditions. These achievements embody a forward-looking theme within chemistry, reduced dependence on protection/deprotection protocols, and opportunities to extend this method to other electrophiles, such as nitroso compounds, and other diketones, such as 3-keto-substituted cyclobutanones, likely exist. Of further significance, the product features of rich functional group diversity combined with a remote stereogenic center may expand tactical application possibilities for more step-efficient approaches to complex biomolecules. A first-generation example of this is our formal synthesis of Alzheimer's γ-secretase modulator drug candidates in the highest yielding synthesis reported to date. It is also clear that new doors have been opened for drug-discovery opportunities within Alzheimer's drug discovery research. Moreover, we propose that unraveling ketolactones **13** into intermediates based on a central chiral methine unit, like that found in keto ester amide **18**, may be a logical starting point for the preparation of artificial chiral cavities, as used in supramolecular host–guest chemistry,[45] or for generating, by dendritic extension, chiral tertiary macromolecules reminiscent of protein environments.[46]

Experimental Section

General synthesis of aldol products 11: TBDPSO-4-hydroxyproline (5.54 mg, 0.015 mmol, 2.0 mol%) was added to a gently stirred solution of the diketone (**6**–**8**; 1.12 mmol, 1.5 equiv) and the aldehyde (0.75 mmol, 1.0 equiv). Upon dissolution, water (40.5 μL, 3.0 equiv) was added. This mixture was stirred at room temperature in a closed reaction vessel until an aldehyde conversion of $\geq$95% could be confirmed by ^{1}H NMR spectroscopy (see the Supporting Information for the exact reaction times with individual compounds; note that extension of the indicated reaction times is often detrimental due to decreased diastereoselectivity from α-keto epimerization). The reaction was worked up by repeated extraction with CH_2Cl_2 or EtOAc (6×10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure ($T<30\,^\circ$C). The crude residue was then exposed to high vacuum for 2–4 h before treatment in the next reaction step to form **13** or **15**. Full experimental details are provided in the Supporting Information.[47]

Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft (award no. NU235/6-1) and by Jacobs University Bremen. We are very thankful for low- and high-resolution mass spectrometry measurements provided by Professor Dr. Nikolai Kuhnert. The authors thank Prof. Dr. Jens Beckmann (University of Bremen) for X-ray analysis of keto-acetonide **15i**. We thank Professor Dr. Heiko Ihmels (University Siegen) for initial CD discussions. We thank Dr. Richard Friary for insightful comments regarding style and conciseness.

Keywords: Alzheimer's disease · diketones · enamines · enantioselective aldol · gamma-secretase modulator · site selectivity

[1] P. M. Tadross, E. N. Jacobsen, *Nat. Chem.* **2012**, *4*, 963–965.
[2] B. C. Wilcock, B. E. Uno, G. L. Bromann, M. J. Clark, T. M. Anderson, M. D. Burke, *Nat. Chem.* **2012**, *4*, 996–1003.
[3] B. S. Fowler, K. M. Laemmerhold, S. J. Miller, *J. Am. Chem. Soc.* **2012**, *134*, 9755–9761.
[4] Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67–70.
[5] K. Matsumoto, M. Mitsuda, N. Ushijima, Y. Demizu, O. Onomura, Y. Matsumura, *Tetrahedron Lett.* **2006**, *47*, 8453–8456.
[6] M. Skoupi, C. Vaxelaire, C. Strohmann, M. Christmann, C. M. Niemeyer, *Chem. Eur. J.* **2015**, *21*, 8701–8705.
[7] a) R. C. Simon, B. Grischek, F. Zepeck, A. Steinreiber, F. Belaj, W. Kroutil, *Angew. Chem. Int. Ed.* **2012**, *51*, 6713–6716; *Angew. Chem.* **2012**, *124*, 6817–6820; b) R. C. Simon, F. Zepeck, W. Kroutil, *Chem. Eur. J.* **2013**, *19*, 2859–2865.
[8] a) J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 7498–7499; b) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658; *Angew. Chem.* **2008**, *120*, 7768–7771.
[9] For an example of a product with double aldol site selectivity, see Table 2, entry 8, compound **3h** (10 mol% catalyst loading, 67% yield, 9:1 d.r., 81% *ee*) in: Y. Shimoda, T. Kubo, M. Sugiura, S. Kotani, M. Nakajima, *Angew. Chem. Int. Ed.* **2013**, *52*, 3461–3464; *Angew. Chem.* **2013**, *125*, 3545–3548.
[10] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[11] B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.
[12] B. Bradshaw, J. Bonjoch, *Synlett* **2012**, *23*, 337–356.
[13] C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; *Angew. Chem.* **2008**, *120*, 44–50.
[14] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207–222.
[15] D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.

[16] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573 – 575.
[17] a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260 – 5267; b) Y. Sekiguchi, A. Sasaoka, A. Shimomoto, S. Fujioka, H. Kotsuki, *Synlett* **2003**, 1655 – 1658; c) Y.-Y. Peng, Q.-P. Ding, Z. Li, P. G. Wang, J.-P. Cheng, *Tetrahedron Lett.* **2003**, *44*, 3871 – 3875.
[18] a) J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543 – 4545; b) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285 – 9289.
[19] a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *45*, 958 – 961; *Angew. Chem.* **2006**, *118*, 972 – 975; b) S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246 – 10256.
[20] D. Sánchez, D. Bastida, J. Burés, C. Isart, O. Pineda, J. Vilarrasa, *Org. Lett.* **2012**, *14*, 536 – 539.
[21] See the abstract and Figure 4 A in: N. Gertsik, D.-M. Chau, Y.-M. Li, *ACS Chem. Biol.* **2015**, *10*, 1925 – 1931.
[22] Y. Garcia, J. C. Hannam, T. Harrison, C. L. Hamblett, J. L. Hubbs, J. J. Kulagowski, A. Madin, M. P. Ridgill, E. Seward (Merck Sharp & Dohme Limited), US 8389547 B2, **2013**.
[23] A. Hall, R. L. Elliott, G. M. P. Giblin, I. Hussain, J. Musgrave, A. Naylor, R. Sasse, B. Smith, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1306 – 1311.
[24] J. E. Baldwin, M. J. Lusch, *Tetrahedron* **1982**, *38*, 2939 – 2947.
[25] C. D. Johnson, *Acc. Chem. Res.* **1993**, *26*, 476 – 482.
[26] N. Itagaki, M. Kimura, T. Sugahara, Y. Iwabuchi, *Org. Lett.* **2005**, *7*, 4185 – 4188.
[27] It is more often than not that cyclohexanone-based aldol products undergo partial, nonselective epimerization upon exposure to silica gel. See the Supporting Information of: T. C. Nugent, M. N. Umar, A. Bibi, *Org. Biomol. Chem.* **2010**, *8*, 4085 – 4089.
[28] a) M. Renz, B. Meunier, *Eur. J. Org. Chem.* **1999**, 737 – 750; b) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Chem. Rev.* **2004**, *104*, 4105 – 4123.
[29] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560 – 3578.
[30] S. H. J. Thompson, M. F. Mahon, K. C. Molloy, M. S. Hadley, T. Gallagher, *J. Chem. Soc. Perkin Trans. 1* **1995**, 379 – 383.
[31] Three reaction steps are required to form the keto-acetonides **15**, among which the reduction step to form the keto-1,3-diols **14** was the lowest yielding, with the major keto-1,3-diol obtained in approximately 70% yield. The most often-formed byproduct was not from reduction of the acyclic ketone but from reduction of the cyclohexanone carbonyl moiety, presumably from the α face. See the Supporting Information for further details.
[32] C. Wu, X. Fu, S. Li, *Tetrahedron* **2011**, *67*, 4283 – 4290.
[33] a) C. Wu, X. Fu, S. Li, *Eur. J. Org. Chem.* **2011**, 1291 – 1299; b) G. N. Ma, A. Bartoszewicz, I. Ibrahem, A. Cordova, *Adv. Synth. Catal.* **2011**, *353*, 3114 – 3122.
[34] a) J. Jiang, L. He, S. W. Luo, L. F. Cun, L. Z. Gong, *Chem. Commun.* **2007**, 736 – 738; b) S. Luo, H. Xu, J. Li, L. Zhang, X. Mi, X. Zheng, J.-P. Cheng, *Tetrahedron* **2007**, *63*, 11307 – 11314; c) F. Giacalone, M. Gruttadauria, P. L. Meo, S. Riela, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 2747 – 2760; d) S. Li, C. Wu, X. Long, X. Fu, G. Chen, Z. Liu, *Catal. Sci. Technol.* **2012**, *2*, 1068 – 1071.
[35] a) B. Rodríguez, A. Bruckmann, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 4710 – 4722; b) X. Companyó, G. Valero, L. Crovetto, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 6564 – 6568.
[36] J. Hardy, D. J. Selkoe, *Science* **2002**, *297*, 353 – 356.
[37] B. Kretner, A. Fukumori, A. Gutsmiedl, R. M. Page, T. Luebbers, G. Galley, K. Baumann, C. Haass, H. Steiner, *J. Biol. Chem.* **2011**, *286*, 15240 – 15251.
[38] T. Li, Y. Huang, S. Jin, L. Ye, N. Rong, X. Yang, Y. Ding, Z. Cheng, J. Zhang, Z. Wan, D. C. Harrison, I. Hussain, A. Hall, D. H. S. Lee, L.-F. Lau, Y. Matsuoka, *J. Neurochem.* **2012**, *121*, 277 – 286.
[39] J. C. Hannam, J. J. Kulagowski, A. Madin, M. P. Ridgill, E. M. Seward (Merck Sharp & Dohme Limited), WO 2006043064 A1, **2006**.
[40] Note: Instead of showing the Merck Sharp & Dohme structure **22** (Scheme 2 of this article), the GSM-1 label is used, see: S. Ousson, A. Saric, A. Baguet, C. Losberger, S. Genoud, F. Vilbois, B. Permanne, I. Hussain, D. Beher, *J. Neurochem.* **2013**, *125*, 610 – 619.
[41] Y. Ohki, T. Higo, K. Uemura, N. Shimada, S. Osawa, O. Berezovska, S. Yokoshima, T. Fukuyama, T. Tomita, T. Iwatsubo, *EMBO J.* **2011**, *30*, 4815 – 4824.
[42] T. K. Chakraborty, A. Ghosh, *Synlett* **2002**, 2039 – 2040.
[43] L.-H. Zhang, G. S. Kauffman, J. A. Pesti, J. Yin, *J. Org. Chem.* **1997**, *62*, 6918 – 6920.
[44] D. A. Evans, K. A. Scheidt, C. W. Downey, *Org. Lett.* **2001**, *3*, 3009 – 3012.
[45] K. I. Assaf, W. M. Nau, *Chem. Soc. Rev.* **2015**, *44*, 394 – 418.
[46] R. Roy, T. C. Shiao, *Chem. Soc. Rev.* **2015**, *44*, 3924 – 3941.
[47] CCDC 1427190 (**15i**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: June 17, 2016
Published online on ■■ ■■, 0000

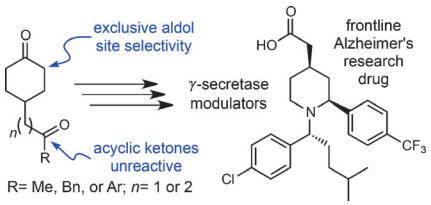
FULL PAPER

Diketone Site Selectivity

T. C. Nugent, F. T. Najafian, H. A. E. D. Hussein, I. Hussain*

■■ – ■■

Beyond Chemoselectivity: Catalytic Site-Selective Aldolization of Diketones and Exploitation for Enantioselective Alzheimer's Drug Candidate Synthesis



Let your enamines play: Ketone site selectivity for cyclohexanone-based diketones has been firmly established and permits a high yielding synthesis of a γ-secretase modulator (GSM). The achievements embody a forward-looking theme within chemistry; reduced dependence on protection/deprotection protocols for increased step efficiency in biomolecule synthesis.