Journal Pre-proof

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PII: S0040-4020(19)31332-8

DOI: https://doi.org/10.1016/j.tet.2019.130913

Reference: TET 130913

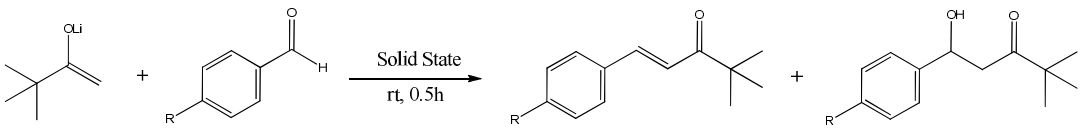
To appear in: *Tetrahedron*

Received Date: 1 July 2019

Revised Date: 19 December 2019

Accepted Date: 20 December 2019

Please cite this article as: Pang H, Williard PG, Solid state aldol reactions of solvated and unsolvated lithium pinacolone enolate aggregates, *Tetrahedron* (2020), doi: https://doi.org/10.1016/j.tet.2019.130913.



Solid State Aldol Reactions of Solvated and Unsolvated Lithium Pinacolone Enolate Aggregates

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Abstract: We reported the first systematic study of the solid-state aldol reactions of solvated and unsolvated lithium pinacolone enolate with a variety of solid aromatic aldehydes utilizing a mortar and pestle condition in comparison with the simple ball milling condition or tetrahydrofuran (THF) solution condition. In solution, the reactions are highly-selective with the aldol condensation product at room temperature. Under the condition of mortar and pestle, the reactions with unsolvated lithium pinacolone enolate showed the mixture of aldol condensation product and aldol addition product at room temperature. With the usage of solvated lithium pinacolone enolate, higher yields for most substrates were obtained. Furthermore, repeating the reactions under a simple ball billing condition with no other precautions at room temperature, we achieved high selectivity and yield of products for all substrates, indicating the powerful ability and the utility of solid-state, mechanochemical aldol reaction conditions.

Introduction

Aldol and related reactions are perhaps the most widely utilized carbon-carbon bond forming reactions in organic chemistry. Despite the general utility of these reactions only a few previous studies report that solvent free reaction conditions yield aldol products, aldol condensation products or aldol-Tishchenko reaction products and often mixtures thereof.[1] In this study we focus on controlling parameters such as

[1] (a) Sharma, D. K.; Singh, B.; Mukherjee, D. Aldol reaction of kojic acid using alumina supported base catalyst and enzymatic resolution of the aldol adduct by CALB. *Tet. Let.* **2014,** *55*, 5846-5850. (b) Banon-Caballero, A.; Guillena, G.; Najera, C., Solvent-free enantioselective organocatalyzed aldol reactions. *Mini-Reviews in Organic Chemistry* **2014,** *11*, 118-128. (c) Niu, F.; Zhang, L.; Luo, S.-Z.; Song, W.-G. Room temperature aldol reactions using magnetic Fe_3O_4@$Fe(OH)_3$ composite microspheres in hydrogen bond catalysis. *Chem. Commun. (Cambridge, United Kingdom)* **2010,** *46*, 1109-1111. (d) Rodriguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C., Solvent-free carbon-carbon bond formations in

stoichiometry, time, reagent composition and reaction protocol to assess their influence on the yield and selectivity of formation of aldol reaction products of the lithium enolate of pinacolone utilizing a simple mechanochemical protocol. Specifically, this study correlates the solvation state and the aggregation state of the lithium enolate of *t*-butyl methyl ketone by starting with a solid enolate of rigorously known composition and solvation to access the selectivity for formation of the aforementioned products upon reaction with some aromatic aldehydes.

Preparative mechanochemical reactions typically imply milling, *e.g.* ball, vibration, attritor or planetary, although alternatives such as screw extrusion and shearing are known.[2] The advantages and drawbacks of preparative mechanochemistry as well as the scope of different reaction types are concisely elucidated in a 2013 issue of *Chemical Reviews* devoted exclusively to this topic and more recently in a 2017

ball mills. *Adv. Synthesis & Catalysis* **2007,** *349*, 2213-2233. (e) Rodriguez, B.; Bruckmann, A.; Bolm, C., A highly efficient asymmetric organocatalytic aldol reaction in a ball mill. *Chem. - A European Journal* **2007,** *13*, 4710-4722. (f) Kaupp, G., Stereoselective thermal solid state reactions. *Topics in Stereochemistry* **2006,** *25*, 303-354. (g) Raston, C. L.; Scott, J. L. Chemoselective, solvent-free aldol condensation reaction. *Green Chem.* **2000**, *2, (2)*, 49-52. (h) Tanaka, K.; Toda, F., Solvent-free organic synthesis. *Chem. Rev. (Washington, D. C.)* **2000,** *100*, 1025-1074. (i) Toda, F.; Tanaka, K.; Hamai, K., Aldol condensations in the absence of solvent: acceleration of the reaction and enhancement of the stereoselectivity. *J. Chem. Soc, Perkin 1* **1990**, 3207-3209.

[2] (a) Quaresma, S.; Andre, V.; Fernandes, A.; Duarte, M. T. Mechanochemistry - A green synthetic methodology leading to metallodrugs, metallopharmaceuticals and bio-inspired metal-organic frameworks. *Inorg. Chim. Acta* **2017**, *455, (Part_2)*, 309-318. (b) Hernandez, J. G.; Bolm, C. Altering product selectivity by mechanochemistry. *J. Org. Chem.* **2017**, *82, (8)*, 4007-4019. (c) Do, J.-L.; Friscic, T. Chemistry 2.0: Developing a New, Solvent-free system of chemical synthesis based on mechanochemistry. *Synlett* **2017**, *28, (16)*, 2066-2092. (d) Tan, D.; Loots, L.; Friscic, T. Towards medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). *Chem. Commun. (Cambridge, U. K.)* **2016**, *52, (50)*, 7760-7781. (e) Hernandez, J. G.; Friscic, T. Metal-catalyzed organic reactions using mechanochemistry. *Tetrahedron Lett.* **2015**, *56, (29)*, 4253-4265. (f) Takacs, L. The historical development of mechanochemistry. *Chem. Soc. Rev.* **2013**, *42, (18)*, 7649-7659. (g) Craig, S. L. Mechanochemistry: A tour of force *Nature (London, U. K.)* **2012**, *487, (7406)*, 176-177. (h) Kaupp, G. Stereoselective thermal solid-state reactions. *Top. Stereochem.* **2006**, *25,* 303-350.

Journal of Organic Chemistry perspective.[3] In this manuscript, we emphasize the influence of solvation of the pinacolone enolate in small scale reactions that are routinely performed without any special milling equipment.

The major potential advantages of solvent-free and solid-state reactions are that they are significantly less sensitive to moisture, are routinely performed at room temperature and usually do not require an inert, dry atmosphere or rigorously purified, dry solvents. Thus, performing aldol reactions under mechanochemical conditions eliminates the use of bulk solvents but also mitigates significant safety concerns in handling bulk solutions of very reactive alkali metal organic compounds under inert and frequently sub-ambient temperature. Atmospheric moisture seems to have little effect on solvent-free and/or mechanochemical aldol-type reactions mainly because ambient water is at the ppm level.[4]

RESULTS AND DISCUSSION

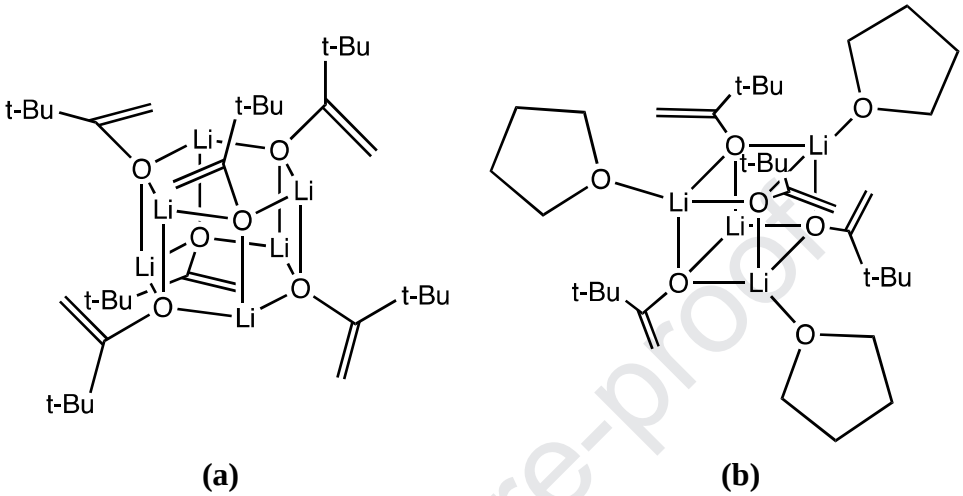
This study of aldol reactions utilizes the lithium enolate of pinacolone as the nucleophile because we can precisely control its aggregation and solvation state. Hence unsolvated lithium pinacolone enolate **1** (unsolvated) was prepared as a white solid by treating pinacolone with freshly made LDA in pentane at 0° C per an established protocol.[5] Our previous x-ray crystallographic study revealed that the

[3] (a) James, S. L.; Friscic, T. Mechanochemistry. *Chem. Soc. Rev.* **2013**, *42, (18)*, 7494-7496. (b) Boldyreva, E. Mechanochemistry of inorganic and organic systems: what is similar, what is different? *Chem. Soc. Rev.* **2013**, *42, (18)*, 7719-7738. (c) Hopgood, H.; Mack, J. "An increased understanding of enolate additions under mechanochemical conditions". *Molecules* **2017**, *22, (5)*, 6961-6967.

[4] Waddell, D. C.; Clark, T. D.; Mack, J. Conducting moisture sensitive reactions under mechanochemical conditions. *Tetrahedron Lett.* **2012**, *53, (34)*, 4510-4513.

[5] Williard, P. G.; Carpenter, G. B., X-ray crystal structure of an unsolvated lithium enolate anion. *J. Am. Chem. Soc.* **1985**, *107*, 3345-3346.

enolate **1** (unsolvated) exists as a hexameric aggregate having a Li_6O_6 core structure illustrated in Figure 1a. Six lithium and six oxygen atoms of the enolate hexamer occupy alternatively the twelve corners of a hexagonal prism. Each lithium atom is surrounded by three enolate oxygens.



(a) **(b)**

Figure 1. Lithium enolate aggregates derived from pinacolone

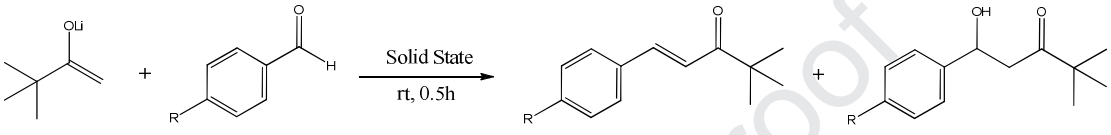
Alternatively, crystallization from THF and pentane solution yields a THF-solvated lithium pinacolone enolate as a tetrameric aggregate depicted in Figure 1b as **1** (solvated).[6] The tetrameric aggregate of **1** (solvated) is an almost perfect cube with vertices consisting of four lithium and four oxygen atoms. The lithium atoms are each surrounded by one THF oxygen and three enolate oxygens so that a distorted tetrahedral coordination sphere results. Hence utilizing these different aggregates of unsolvated and THF-solvated pinacolone enolate, entirely different reactants initiate solid state reactions described below.

Initially we investigated solid-state, mechanochemical aldol reactions utilizing the hexameric enolate **1** (unsolvated) using an agate mortar and pestle and manual grinding. With a goal to optimize the yield of the products of the reaction of this unsolvated enolate with either *p*-Cl-benzaldehyde or *p*-Br-benzaldehyde, we report

[6] Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D., Tetrameric cubic structures of two solvated lithium enolates. *Helvetica Chimica Acta* **1981,** *64*, 2617-2621.

the results of changing the ratio of enolate to the aldehyde electrophiles shown in Table 1. All of reactions were carried out as described above using ratios of unsolvated pinacolone enolate **1** to 4-halobenzaldehydes **2a** or **2b**, ranging from 1.2:1 to 2:1 (Table 1). These results clearly show that there is a specific ratio of enolate to electrophile required to optimize the yield of products, *i.e.* 1.2:1.

Table 1. Effect of the ratio of reactants on the solid state aldol reaction between pinacolone enolate 1 (unsolvated) and p-halo-benzaldeydes (2a and 2b)



1(unsolvated) **2a:** R = Cl **2b:** R = Br **3a:** R = Cl **3b:** R = Br **4a:** R = Cl **4b:** R = Br

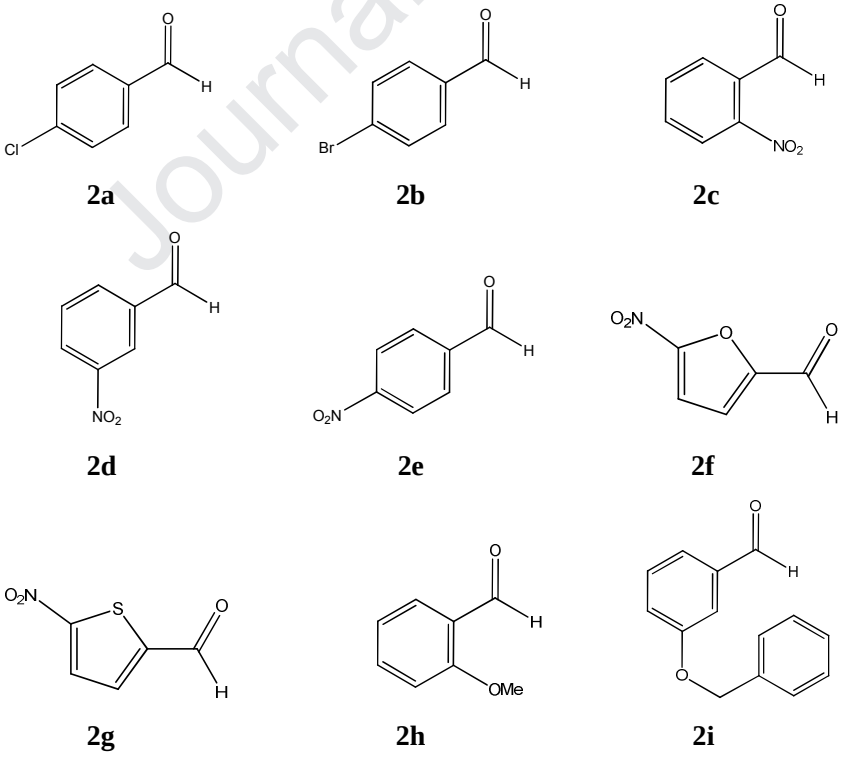
Entry	Aldehyde	**1** (unsolvated)/**2**	Conversion (%)	Yield(%) **3**	Yield (%) **4**	Total Yield (%)
1	**2a**	1.2:1.0	98	41	45	86
2	**2a**	1.6:1.0	>99	34	29	63
3	**2a**	2.0:1.0	>99	35	26	61
4	**2b**	1.2:1.0	97	20	25	45
5	**2b**	1.6:1.0	>99	20	14	34
6	**2b**	2.0:1.0	>99	12	15	27

Reactions were conducted on a 2.0 mmol scale for 0.5h at room temperature using mortar and pestle. Isolated yields of products after column chromatography are reported.

The first noteworthy observation is that the solid-state aldol reaction using mortar and pestle resulted in complete conversion of the aldehyde **2a** into products. When 2 full equivalents of pinacolone enolate were used, the aldol condensation product **3a** and the aldol addition product **4a** were obtained in 35% and 26% isolated yield respectively (Table 1, entry 3). It is also noteworthy that the isolated yields of both **3a** and **4a** differ slightly as the stoichiometry of enolate decreased from 2.0 to 1.6 equivalents (entry 2). The optimum combined yield of 86% of aldol and condensation products was achieved by using 1.2 equivalents of unsolvated

pinacolone enolate (entry 1). Similar results were obtained when 4-bromobenzaldehyde **2b** was employed (entry 4). With aldehyde **2b**, we observed that the best combined yield (45%) was also obtained using 1.2 equivalents of pinacolone enolate. Use of more than 1.6 equivalents of enolate led to a dramatic decrease in the combined yield of aldol condensation product and aldol addition product. We found that yields of aldol and condensation products **3** and **4** were lowered due to the Michael addition reaction of excess enolate to the aldol condensation product as seen in the crude NMR spectra of the reaction mixtures although these Michael addition products were not purified and isolated. Thus, with a higher ratio of enolate to aldehyde, the conversion of the aldehyde (**2a** and **2b**) can be increased but at the same time, Michael addition of excess enolate to **3b** is more favorable. Based on the results in Table 1, subsequent experiments were limited to an enolate to aldehyde ratio of 1.2:1.

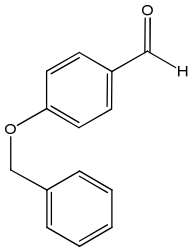
Figure 2. Structures of substituted aldehydes in aldol reaction



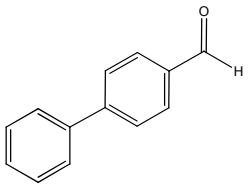
2a **2b** **2c**

2d **2e** **2f**

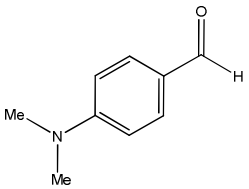
2g **2h** **2i**



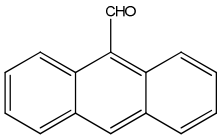
2j



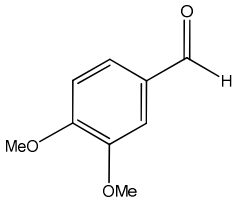
2k



2l



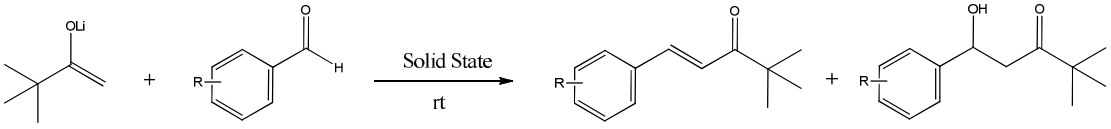
2m



2n

The aldol derived product yields are significantly influenced by the electronic nature of the substitution in the aldehyde **2** (Figure 2 and Table 2). Electron withdrawing groups on the *para* or *ortho* position of the benzene ring (Table 2, entries 1-6, 9-10) leads to reactions being completed in shorter time, while the electron-donating groups, such as benzyloxy (entries 19-20), phenyl (entries 21-22), and dimethylamino (entries 23-24) lead to reactions being completed in longer time utilizing either unsolvated enolate or THF solvated enolate. This observations mirror expected reactivity differences among the differing electrophiles. It is also noteworthy that yields of products with electrophiles depicted in entries 17-28 of Table 2 are improved by lengthening the reaction times to 1h instead of 0.5h. The longer reaction times also result in a higher ratio of aldol condensation product to aldol addition product.

Table 2. Scope of the aldol reaction of the lithium pinacolone enolate (1) to aldehydes (2) in the solid state using mortar and pestle



1 **2(a-n)** **3(a-n)** **4(a-n)**

Entry	Enolate	Aldehyde	Time (h)	Yield **3** (%)	Yield **4** (%)	Total Yield (%)

1[a]	**1** (solvated)	**2a**	0.5	45	43	88
2[a]	**1** (solvated)	**2b**	0.5	32	28	60
3[b]	**1** (unsolvated)	**2c**	0.5	7	18	25
4[b]	**1** (solvated)	**2c**	0.5	9	51	60
5[b]	**1** (unsolvated)	**2d**	0.5	10	10	20
6[b]	**1** (solvated)	**2d**	0.5	6	16	22
7[b]	**1** (unsolvated)	**2e**	0.5	5	3	8
8[b]	**1** (solvated)	**2e**	0.5	5	4	9
9	**1** (unsolvated)	**2f**	0.5	4	20	24
10	**1** (solvated)	**2f**	0.5	9	24	33
11	**1** (unsolvated)	**2g**	0.5	8	25	33
12	**1** (solvated)	**2g**	0.5	12	28	40
13	**1** (unsolvated)	**2h**	0.5	20	19	39
14	**1** (solvated)	**2h**	0.5	23	27	50
15[a]	**1** (unsolvated)	**2i**	1	17	8	25
16[a]	**1** (solvated)	**2i**	1	22	11	33
17	**1** (unsolvated)	**2j**	1	42	8	50

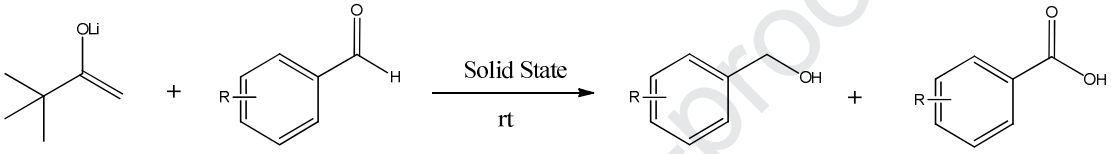
18	**1** (solvated)	**2j**	1	54	10	64
19[a]	**1** (unsolvated)	**2k**	1	32	8	40
20[a]	**1** (solvated)	**2k**	1	34	24	58
21	**1** (unsolvated)	**2l**	1	38	9	47
22	**1** (solvated)	**2l**	1	50	11	61
23	**1** (unsolvated)	**2m**	1	42	2	44
24	**1** (solvated)	**2m**	1	50	10	60
25[a]	**1** (unsolvated)	**2n**	1	41	3	44
26[a]	**1** (solvated)	**2n**	1	40	10	50

Reactions were conducted on a 2.0 mmol scale for 0.5h-1h at room temperature using mortar and pestle. Isolated yields of products after column chromatography are reported. [a]Aldol-Tishchenko reaction was detected (*vide infra*). [b]The major reaction pathway is the Cannizzaro reaction.

From Table 1, entries 1 and 4, we note that reaction of unsolvated lithium enolate **1** with aldehydes with a chloro or bromo substituent at the para position yield aldol condensation products **3** and aldol addition products **4** in moderate yields. The methoxy group at the ortho position of the benzene ring resulted in a combination of aldol condensation product and aldol addition product in 39% yield (Table 2, entry 13). With two methoxy groups at the *meta* and *para* position of the benzene ring, a similar total yield of 44% was observed (entry 25). Regardless of the electronic character, a substituent at *meta* position of the benzene ring had little impact on the total yield of the reaction. However, a longer reaction time always yielded more aldol condensation than aldol addition product. The *para* benzyloxy group on the benzaldehyde produced a higher yield than the *meta* benzyloxy group (entries 15 and 17). Products with a *p*-phenyl- and *p*-dimethylamino- substituted rings were

obtained in similar yields (entries 19 and 21). Moreover, 9-anthraldehyde was also compatible with the reaction conditions and lead to moderate yield (entry 23). Quite surprisingly, the strongly electron-withdrawing nitro group resulted in a low reaction yield regardless of its position on the ring (entries 3, 5, 7, 9 and 11). With this strongly electron withdrawing substituent, we observed that Cannizzaro reaction product predominated relative to the aldol reaction products shown in Table 3.

Table 3. Cannizzaro reaction between the lithium pinacolone enolate (1) and some aldehydes (2) in the solid state using mortar and pestle



1 **2(c-e)** **5(c-e)** **6(c-e)**

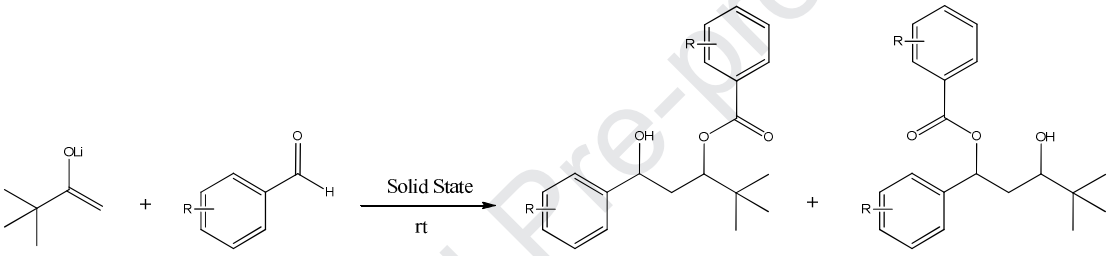
Entry	Enolate	Aldehyde	Time (h)	Yield **5** (%)	Yield **6** (%)
1	**1** (unsolvated)	**2c**	0.5	55	51
2	**1** (solvated)	**2c**	0.5	18	15
3	**1** (unsolvated)	**2d**	0.5	66	61
4	**1** (solvated)	**2d**	0.5	58	54
5	**1** (unsolvated)	**2e**	0.5	73	69
6	**1** (solvated)	**2e**	0.5	70	67

Reactions were conducted on a 2.0 mmol scale for 0.5h at room temperature using mortar and pestle. The ratio of alcohol and carboxylic acid should be identical. The yields reported above are calculated by assuming that the starting aldehyde theoretically yields half an equivalent of each product and are reported after column chromatography.

We suspected that atmospheric moisture was a factor decreasing the yields of addition

and condensation products. The presence of even trace quantities of water can lead to observation of Cannizzaro reaction products by offering a source of hydroxide generated from the reaction of lithium enolate especially since no special precautions were taken to conduct these reactions in an inert atmosphere. It is also noteworthy that an aldol-Tishchenko reaction[7] was also detected for some substrates (Table 4). In this process, the lithiated aldolate adduct reacts with one additional equivalent of aldehyde to effect Tishchenko reaction ultimately forming products **7** and **8**.[8]

Table 4. Aldol-Tishchenko reaction between the lithium pinacolone enolate (1) and some aldehydes (2) in the solid state using mortar and pestle



1 **2(a,b,i,k,n)** **7(a,b,i,k,n)** **8(a,b,i,k,n)**

Entry	Enolate	Aldehyde	Time (h)	Yield **7** (%)	Yield **8** (%)	Total Yield (%)
1	**1** (unsolvated)	**2a**	0.5	3	10	13
2	**1** (solvated)	**2a**	0.5	3	8	11
3	**1** (unsolvated)	**2b**	0.5	5	23	28

[7] (a) Nishiura, M.; Kameoka, M.; Imamoto, T., Michael and tandem Aldol-Tischenko reactions catalyzed by samarium(III) aryloxide complexes. *Kidorui* **2000,** *36*, 294-295. (b) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A., Tandem Aldol-Tishchenko Reactions of Lithium Enolates: A Highly Stereoselective Method for Diol and Triol Synthesis. *J. Org. Chem.* **1997,** *62*, 5674-5675.

[8] Evans, D. A.; Hoveyda, A. H., Samarium-catalyzed intramolecular Tishchenko reduction of b-hydroxy ketones. A stereoselective approach to the synthesis of differentiated anti 1,3-diol monoesters. *J. Am. Chem. Soc.* **1990,** *112*, 6447-6449.

4	**1** (solvated)	**2b**	0.5	5	20	25
5	**1** (unsolvated)	**2i**	1	-	15	15
6	**1** (solvated)	**2i**	1	-	10	10
7	**1** (unsolvated)	**2k**	1	4	21	25
8	**1** (solvated)	**2k**	1	6	14	20
9	**1** (unsolvated)	**2n**	1	-	12	12
10	**1** (solvated)	**2n**	1	-	10	10

Reactions were conducted on a 2.0 mmol scale for 0.5 h-1h at room temperature using mortar and pestle. Isolated yields of products after column chromatography are reported.

Our next comparison focuses on the solvated lithium pinacolone enolate also shown in Table 2. Based upon analogy with solution phase enolate reactions in THF solution, we anticipated that smaller aggregates may react faster than larger aggregates.[9] Hence solvated enolate **1** (solvated) appears to react more rapidly and proceed with improved yields with the same high conversion. Aldehydes with a chloro- or bromo-group at the *para* position of the benzene ring lead to improved yields (Table 2, entries 1 and 2). The *ortho* methoxy- and *meta*, *para* dimethoxy- substitued rings were similarly observed to produce higher total yields (entries 13, 14, 25 and 26). Importantly, for those aldehydes with low reactivity, the use of highly-reactive solvated enolate **1** (solvated) improves the total yields by about 10-20% (entries 17-24). To our surprise, for the aldehyde with a nitro group on *ortho* position, a large improvement in yield (35%) was obtained (entries 3 and 4). However, for other benzaldehydes with a nitro substituent, THF-solvated enolate has little impact on the

[9] Kolonko, K. J.; Wherritt, D. J.; Reich, H. J., Mechanistic studies of the lithium enolate of 4-fluoroacetophenone: Rapid-injection NMR study of enolate formation, dynamics, and aldol reactivity. *J. Am. Chem. Soc.* **2011,** *133*, 16774-16777.

total yield of aldol and condensation products because the Cannizzaro reaction dominates the product mixture - see Table 2 entries 6 and 8 and Table 3 entries 4 and 6. The low yields for most aldehydes with a nitro group prompted us to seek optimize reaction conditions for reactants with strong electron drawing substituents.

We now turned our attention to the reaction protocol itself. Ball milling is a mechanochemical technique, which can be applied as an alternative method of manual grinding in a mortar and pestle. The most trivial ball milling procedure we utilized involves milling of the solid reactants with inert glass balls in a rotating vial secured to the rotating shaft of a rotatory evaporator although there are many more sophisticated variations available.[10] Previous studies have shown that enolate chemistry using a mortar and pestle in open atmosphere gives lower yields of products than utilizing sealed ball milling conditions presumably because of the presence of atmospheric moisture.[11] Since our ball mill analog reactions in a vial on a rotary evaporator are not open, contact with atmospheric moisture is limited and the level of the water is constant at the ppm level. Although no special precaution was taken to rigorously exclude moisture and the enolates were generated *in situ* in all of the previous studies, the conjugate acid of the base utilized to generate the enolate was always present in these reactions reported previously. This feature distinguishes our results reported from all previously reported mechanochemical aldol reactions since we initiate all of our reactions utilizing pure precipitated or crystallized enolates.

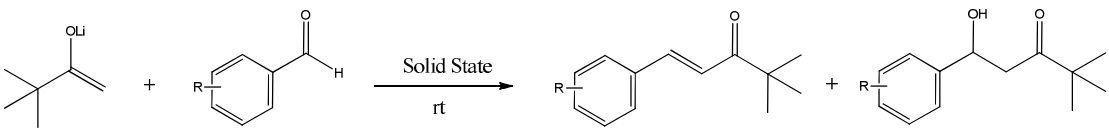
Hence to assess the effect of conducting reactions in the open atmosphere relative to

[10] (a) Rodriguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C., Solvent-free carbon-carbon bond formations in ball mills. *Advanced Synthesis & Catalysis* **2007,** *349*, 2213-2233. (b) Rodriguez, B.; Bruckmann, A.; Bolm, C., A highly efficient asymmetric organocatalytic aldol reaction in a ball mill. *Chemistry - A European Journal* **2007,** *13*, 4710-4722. (c) Rodriguez, B.; Rantanen, T.; Bolm, C., Solvent-free asymmetric organocatalysis in a ball mill. *Angew. Chem., Int.l Ed.* **2006,** *45*, 6924-6926.

[11] (a) Toda, F.; Kiyoshige, K.; Yagi, M., Solid-state reduction of ketones with sodium borohydride. *Angewandte Chemie* **1989**, *101*, 329-330. (b) Waddell, D. C.; Clark, T. D.; Mack, J., Conducting moisture sensitive reactions under mechanochemical conditions. *Tetrahedron Letters* **2012**, *53*, 4510-4513.

conducting the reactions in a controlled atmosphere, we repeated all the reactions with unsolvated lithium enolate **1** (unsolvated) and aldehydes **2** in a pre-dried sealed vial using the crude ball milling like conditions described above (Table 5). To our gratification, we observed an increased yield of aldol adducts with higher selectivity for the aldol addition product relative to aldol condensation product for all substrates. Thus, aldehydes with chloro group at the *para* position of the benzene ring provided the desired aldol addition product in 74% with high selectivity versus the aldol condensation product (91:9) (entry 1). A similar result was obtained with the use of *para* bromo substrate (entry 2). The highest yield and selectivity are seen utilizing the aldehyde with benzyloxy group at the *meta* position (84%, 95:5) (entry 9). Importantly, for those aldehydes with lower reactivity, the selectivity becomes slightly lower, compared with those aldehydes with high reactivity (entries 11-14). Regardless of the position of the nitro group on the benzene ring, nitro- substituted aldehydes resulted in good yields for aldol addition product with high selectivity (entries 3-7). This observation confirmed that the low yields of products from aldehydes with a nitro substituent could be dramatically improved when moisture is minimized. Thus, under ball milling conditions, even without taking precautions to remove moisture, the unsolvated, hexameric lithium pinacolone enolate preferentially reacts with substituted benzaldehydes to yield aldol products. The most likely explanation for this is that quenching of the enolate by the moisture in the atmosphere is minimized. This also explains why there is a decrease in the relative portion of Cannizzaro reaction product since less hydroxide is present to catalyze the Cannizzaro reaction.

Table 5. Scope of aldol reaction of unsolvated lithium pinacolone enolate 1 to aldehydes 2 in a sealed vial under ball milling conditions



1(unsolvated) **2(a-n)** **3(a-n)** **4(a-n)**

Entry	Aldehyde	Time (h)	Yield **3** (%)	Yield **4** (%)	Selectivity **4:3**
1	**2a**	4	7	74	91:9
2	**2b**	4	5	73	94:6
3	**2c**	6	4	78	95:5
4	**2d**	8	9	69	88:12
5	**2e**	6	4	74	95:5
6	**2f**	12	3	46	94:6
7	**2g**	12	5	52	91:9
8	**2h**	4	12	70	85:15
9	**2i**	12	4	84	95:5
10	**2g**	12	6	57	90:10
11	**2k**	12	19	53	74:26
12	**2l**	12	15	74	83:17
13	**2m**	12	22	69	76:24
14	**2n**	12	8	61	88:12

Reactions were conducted on a 2.0 mmol scale for 4h-12h at room temperature in a sealed vial under ball milling conditions. Isolated yields of products after column chromatography are reported.

For comparison, we contrast the corresponding aldol reactions in solution with

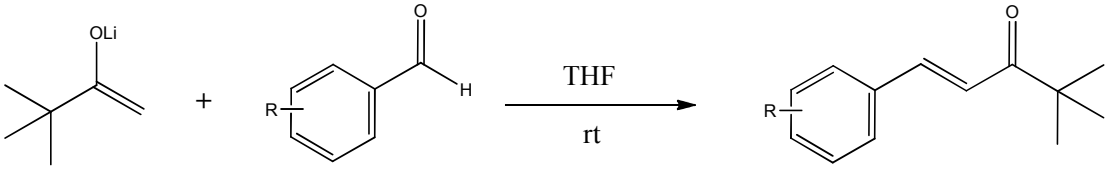
solid-state reactions. As seen in the Table 6, the aldol reaction in solution can generate solely aldol condensation product in a decent yield with high conversions at the room temperature utilizing a pinacolone enolate in THF solution. This solution phase reaction has been studied in detail by others.[12] Although solution phase reactions are typically conducted at -78° C, for our comparative studies we conducted both the solution phase and solid-state reactions at room temperature. Furthermore, our solution phase reactions are complicated by the uncertainty of both the aggregation state and the solvation state of reactive enolate in THF at room temperature.[13] In the solution phase reactions, aldol reaction product was not observed and only aldol condensation product was found.

For most aromatic aldehydes in this study, the total yield of all products under ball milling conditions described above is comparable with the yields in solution although the selectivity of products differs. In many cases, yields under ball milling conditions are higher than yields in solution. The single most significant and important advantage of the mechanochemical reaction conditions is that these reactions can be carried at room temperature on a preparative scale with increased selectivity relative to the ubiquitous solution phase reactions at -78° C. These results indicated the powerful ability and the utility of solid-state, mechanochemical aldol reaction conditions.

[12] (a) Reich, H. J., Role of organolithium aggregates and mixed aggregates in organolithium mechanisms. *Chemical Reviews (Washington, DC, United States)* **2013,** *113*, 7130-7178. (b) Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L. Understanding solid/solid organic reactions. *J. Am. Chem. Soc.* **2001**, *123, (36)*, 8701-8708.

[13] (a) Liou, L. R.; McNeil, A. J.; Ramirez, A.; Toombes, G. E. S.; Gruver, J. M.; Collum, D. B., Lithium enolates of simple ketones: Structure determination using the method of continuous variation. *J. Am. Chem. Soc.* **2008,** *130*, 4859-4868. (b) Gruver, J. M.; Liou, L. R.; McNeil, A. J.; Ramirez, A.; Collum, D. B., Solution structures of lithium enolates, phenolates, carboxylates, and alkoxides in the presence of N,N,N',N'-tetramethylethylenediamine: A prevalence of cyclic dimers. *J. Org. Chem.* **2008,** *73*, 7743-7747.

Table 6. Scope of aldol reaction of the lithium pinacolone enolate 1 (unsolvated) to aldehydes (2) in THF solution



1(unsolvated) **2(a-n)** **3(a-n)**

Entry	Aldehyde	Time (h)	Conversion **2** (%)	Yield **3** (%)
1	**2a**	2	>99	61
2	**2b**	2	>99	55
3	**2c**	2	>99	81
4	**2d**	2	>99	55
5	**2e**	2	>99	66
6	**2f**	2	97	22
7	**2g**	2	98	40
8	**2h**	3	>99	63
9	**2i**	5	>99	62
10	**2j**	5	>99	70
11	**2k**	2	97	83
12	**2l**	2	97	58
13	**2m**	3	98	59

14	**2n**	2	98	50

Reactions were conducted on a 2.0 mmol scale for 2h-5h at room temperature in THF solution. Isolated yields of products after column chromatography are reported.

CONCLUSIONS

We disclose systematic studies of aldol reaction of differently solvated lithium enolate of pinacolone with a variety of aromatic aldehydes using different reaction methods and conditions. In THF solution, aldol reaction of unsolvated lithium pinacolone enolate afforded aldol condensation product in a decent yield along with Michael adduct. However, the same aldol reaction conducted without solvent with a mortar and pestle resulted in a combination of aldol addition product and aldol condensation product. Low yields are seen when utilizing aldehydes with powerful electron withdrawing groups such as a nitro group. The presence of moisture in the mechanochemical reactions resulted in observation of increased selectivity for Cannizzaro reaction product. To obtain optimal yields in the mechanochemical reactions, a THF-solvated pinacolone enolate is preferred leading to improved yield for all substrates other than aldehydes with the strongly electron withdrawing nitro substituent. Furthermore, by using a sealed vial under ball milling conditions without any precautions to remove water, the aldol reactions are all remarkably clean and yield mostly aldol addition product. This is not the major product observed in solution phase reactions or by using a mortar and pestle. Gratifyingly, under the simple ball milling conditions utilizing a sealed vial, glass beads and a rotary evaporator protocol, the aldehydes containing a nitro group resulted in a high yield of aldol addition product as well. Hence the observation of good yields with high selectivity for all substrates under relatively unsophisticated ball milling conditions demonstrates the strong potential for carrying out solid-state enolate reactions such as the aldol reaction. Additionally, it is not necessary to rigorously remove the moisture when utilizing moisture-sensitive, crystalline enolates as reactants in mechanochemical reactions. We anticipate that these reaction conditions are easily scalable. Results reported in this article provide useful initial guidelines for conducting enolate reactions in addition to

the aldol related family of reactions under solid state conditions.

EXPERIMENTAL SECTION

General Methods. Solid state reactions were carried out in either a mortar and pestle or a sealed vial without any special precautions to remove the oxygen and moisture. Reactions in a sealed vial were conducted using the motor unit of the rotary evaporator in horizontal position with a 20 mL glass vial sealed with rubber septum. This instrument rotated at a speed of approximately 200 rpm. The grinding media is 20 balls (5 mm diameter) made of glass. Grinding cycles are repeated during the reaction time. Solution-based reactions were carried out in glassware without nitrogen-protection. Liquid and solutions were transferred via syringe. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz, respectively. Chemical shifts are recorded in parts per million (ppm, δ) downfield using the residual solvent signal of $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR) or DMSO (2.50 ppm for ^{1}H NMR, 39.51 ppm for ^{13}C NMR). Reactions in solution were monitored by thin-layer chromatography on silica gel 60 using UV light (254 nm) as a visualizing agent and hexane/ethyl acetate as developing agent. Purification of products was accomplished by flash chromatography (silica gel 60, particle size 0.04-0.063 mm). Yields were determined after column chromatography.

All reagents were purchased from commercial suppliers. Pentane, diisopropylamine (DIPA) were dried by stirring with calcium hydride (CaH_2) under an Ar atmosphere overnight and then distilled. *p*-Chlorobenzadehyde and *p*-bromobenzaldehyde were purified by crystallizing from EtOH/H_2O(3:1). *o*-Nitrobenzaldehyde was distilled under reduced pressure before use. *m*-Nitrobenzaldehyde and *p*-nitrobenzaldehyde were purified by crystallizing from water. Other purchased aldehydes were dried before use. All aldehydes are in solid phase for the reaction.

Solid phase enolates **1** (unsolvated) and **1** (solvated) were prepared according to described procedures.[5]

General Procedures for Aldol Reaction of Lithium Pinacolone Enolates 1

(unsolvated) or 1 (solvated) to Aldehydes (2) Using Mortar and Pestle. A mixture of excess **1** (unsolvated) or **1** (solvated) (2.4 mmol, 1.2 equiv) and aldehydes **2** (2.0 mmol, 1.0 equiv) was ground with an agate mortar and pestle by hand. After grinding at room temperature for 0.5h (or other time spans as specified) in open air, the reaction mixture was quenched by adding 5.0 mL of saturated NH_4Cl aqueous solution, followed by 15 mL of methylene chloride. The organic layer was separated in a separatory funnel and saved. The aqueous layer was further extracted with methylene chloride (2x10 mL). The combined organic extract was dried over anhydrous Na_2SO_4. Upon removal of the solvent at room temperature under reduced pressure, the crude mixture of products was obtained, and purified by column chromatography (hexane/ethyl acetate).

General Procedures for Aldol Reaction of Unsolvated Lithium Pinacolone Enolate 1 (unsolvated) to Aldehydes (2) under Ball Milling Conditions. A standard vial of approximately 20 mL volume was charged with enolate **1** (unsolvated) (2.4 mmol, 1.2 equiv), aldehydes **2** (2.0 mmol, 1.0 equiv) and 20 glass balls of approximately 0.5 mm diameter. Grinding was started using the ball mill with a rotation speed of 200 rpm. An identical work-up procedure was utilized as for the reactions described above.

General Procedures for Aldol Reaction of Unsolvated Lithium Pinacolone Enolate 1 (unsolvated) to Aldehydes (2) in THF Solution. A solution of enolate **1** (unsolvated) was prepared by dissolving (2.4 mmol, 1.2 equiv) **1** (unsolvated) to 10 mL of THF at room temperature. Aldehydes **2** (2.0 mmol, 1.0 equiv) were added into this 10 mL of THF solution all at once. The reactions were stirred at room temperature and monitored by TLC. After completion of the reaction (2-5h), the mixture was quenched by adding 5.0 mL of saturated NH_4Cl aqueous solution and the identical work-up procedure followed.

(*E*)-1-(4-chlorophenyl)-4,4-dimethylpent-1-en-3-one (3a): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 15.6 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.4

Hz, 2H), 7.09 (d, *J* = 15.6 Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.16, 141.62, 136.18, 133.58, 129.59, 129.27, 121.30, 43.43, 26.42. HRMS (ESI+) m/z calcd for $C_{13}H_{15}OCl + H^+$ 223.0884, found 223.0880.

(*E*)-1-(4-bromophenyl)-4,4-dimethylpent-1-en-3-one (3b): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.60 (d, *J* = 15.6 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 15.6 Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.15, 141.68, 134.03, 132.24, 129.81, 124.52, 121.41, 43.44, 26.42. HRMS (ESI+) m/z calcd for $C_{13}H_{15}OBr + H^+$ 267.0379, found 267.0380.

(*E*)-4,4-dimethyl-1-(2-nitrophenyl)pent-1-en-3-one (3c): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.06 (d, *J* = 15.5 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.58 – 7.49 (m, 1H), 7.00 (d, *J* = 15.5 Hz, 1H), 1.24 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 203.31, 148.78, 138.19, 133.47, 131.39, 130.22, 129.26, 125.63, 124.95, 43.44, 26.20. HRMS (ESI+) m/z calcd for $C_{13}H_{15}O_3N + H^+$ 234.1124, found 234.1117.

(*E*)-4,4-dimethyl-1-(3-nitrophenyl)pent-1-en-3-one (3d): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.43 (s, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 15.6 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 15.6 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 203.75, 148.78, 140.14, 136.83, 134.46, 130.06, 124.52, 123.54, 122.25, 43.54, 26.26. HRMS (ESI+) m/z calcd for $C_{13}H_{15}O_3N + H^+$ 234.1124, found 234.1117.

(*E*)-4,4-dimethyl-1-(4-nitrophenyl)pent-1-en-3-one (3e): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 15.7 Hz, 1H), 7.22 (d, *J* = 15.6 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 203.70, 148.51, 141.28, 140.06, 128.94, 124.63, 124.25, 43.57, 26.24. HRMS (ESI+) m/z calcd for $C_{13}H_{15}O_3N + H^+$ 234.1124, found 234.1121.

(*E*)-4,4-dimethyl-1-(5-nitrofuran-2-yl)pent-1-en-3-one (3f): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.21 (d, *J* = 15.5 Hz, 1H), 7.17 (d, *J* = 3.6 Hz, 1H), 7.10 (d, *J* = 15.1 Hz, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 203.37, 153.31, 152.20, 126.99, 124.51, 116.22, 113.32, 43.60, 26.11. HRMS (ESI+) m/z calcd for $C_{11}H_{13}O_4N + H^+$ 224.0917, found 224.0918.

(*E*)-4,4-dimethyl-1-(5-nitrothiophen-2-yl)pent-1-en-3-one (3g): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.85 (d, *J* = 4.2 Hz, 1H), 7.64 (d, *J* = 15.4 Hz, 1H), 7.20 (d, *J* = 4.2 Hz, 1H), 7.05 (d, *J* = 15.4 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 203.12, 151.86, 146.57, 133.59, 129.46, 129.20, 124.13, 43.51, 26.17. HRMS (ESI+) m/z calcd for $C_{11}H_{13}O_3NS + H^+$ 240.0689, found 240.0697.

(*E*)-1-(2-methoxyphenyl)-4,4-dimethylpent-1-en-3-one (3h): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.00 (d, *J* = 15.8 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.8 Hz,

1H), 7.21 (d, *J* = 15.8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.79, 158.78, 138.36, 131.45, 129.04, 124.12, 121.61, 120.73, 111.27, 55.60, 43.29, 26.52. HRMS (ESI+) m/z calcd for $C_{14}H_{18}O_2 + H^+$ 219.1379, found 219.1378.

(*E*)-1-(3-(benzyloxy)phenyl)-4,4-dimethylpent-1-en-3-one (3i): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.64 (d, *J* = 15.5 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.1 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.21-7.15 (m, 2H), 7.09 (d, *J* = 15.5 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 2H), 1.23 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.32, 159.20, 142.83, 136.81, 136.53, 130.02, 128.80, 128.26, 127.67, 121.38, 121.22, 116.70, 114.61, 70.29, 43.40, 26.43. HRMS (ESI+) m/z calcd for $C_{20}H_{22}O_2 + H^+$ 295.1693, found 295.1705.

(*E*)-1-(4-(benzyloxy)phenyl)-4,4-dimethylpent-1-en-3-one (3j): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.65 (d, *J* = 15.5 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 15.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 5.10 (s, 2H), 1.22 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.38, 160.67, 142.71, 136.65, 130.12, 128.81, 128.29, 128.09, 127.60, 118.77, 115.36, 70.25, 43.29, 26.58. HRMS (ESI+) m/z calcd for $C_{20}H_{22}O_2 + H^+$ 295.1693, found 295.1691.

(*E*)-1-([1,1'-biphenyl]-4-yl)-4,4-dimethylpent-1-en-3-one (3k): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.73 (d, *J* = 15.6 Hz, 1H), 7.68 – 7.60 (m, 6H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 15.6 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.37, 143.11, 142.58, 140.35, 134.05, 129.04, 128.93, 127.96, 127.65, 127.18, 120.73, 43.42, 26.50. HRMS (ESI+) m/z calcd for $C_{19}H_{20}O + H^+$ 265.1587, found 265.1571.

(*E*)-1-(4-(dimethylamino)phenyl)-4,4-dimethylpent-1-en-3-one (3l): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.65 (d, *J* = 15.4 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 15.4 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 3.02 (s, 6H), 1.22 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.57, 151.91, 143.72, 130.19, 122.88, 115.85, 111.95, 43.15, 40.30, 26.79. HRMS (ESI+) m/z calcd for $C_{15}H_{21}NO + H^+$ 232.1696, found 232.1704.

(*E*)-1-(anthracen-9-yl)-4,4-dimethylpent-1-en-3-one (3m): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.64 (d, *J* = 15.9 Hz, 1H), 8.45 (s, 1H), 8.22 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 2H), 7.55 – 7.43 (m, 4H), 7.11 (d, *J* = 15.9 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 203.90, 140.01, 131.43, 130.61, 130.35, 129.71, 129.01, 128.17, 126.38, 125.50, 125.43, 43.45, 26.28. HRMS (ESI+) m/z calcd for $C_{21}H_{20}O + H^+$ 289.1587, found 289.1588.

(*E*)-1-(3,4-dimethoxyphenyl)-4,4-dimethylpent-1-en-3-one (3n): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.63 (d, *J* = 15.5 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.07 (d, *J* = 1.4 Hz, 1H), 6.99 (d, *J* = 15.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 3H),

3.92 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 204.31, 151.24, 149.30, 143.11, 128.06, 122.83, 118.75, 111.23, 110.32, 56.13, 56.12, 43.31, 26.60. HRMS (ESI+) m/z calcd for $C_{15}H_{20}O_3 + H^+$ 249.1485, found 249.1482.

1-(4-chlorophenyl)-1-hydroxy-4,4-dimethylpentan-3-one (4a): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.35-7.27 (m, *J* = 8.6 Hz, 4H), 5.10 (dt, *J* = 7.9, 3.2 Hz, 1H), 3.64 (d, *J* = 2.8 Hz, 1H), 2.89 – 2.76 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 216.92, 141.65, 133.37, 128.76, 127.20, 69.62, 45.45, 44.55, 26.28. HRMS (ESI+) m/z calcd for $C_{13}H_{17}O_2Cl + Na^+$ 263.0809, found 263.0810.

1-(4-bromophenyl)-1-hydroxy-4,4-dimethylpentan-3-one (4b): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.47 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.09 (dt, *J* = 8.1, 3.2 Hz, 1H), 3.63 (d, *J* = 2.9 Hz, 1H), 2.89 – 2.79 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 216.88, 142.19, 131.72, 127.55, 121.47, 69.67, 45.42, 44.55, 26.29. HRMS (ESI+) m/z calcd for $C_{13}H_{17}O_2Br + Na^+$ 307.0304, found 307.0308.

1-hydroxy-4,4-dimethyl-1-(2-nitrophenyl)pentan-3-one (4c): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.96 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 5.59 (d, *J* = 9.2 Hz, 1H), 4.13 (s, 1H), 3.25 (d, *J* = 17.8 Hz, 1H), 2.66 (dd, *J* = 17.8, 9.3 Hz, 1H), 1.16 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.22, 147.27, 138.82, 133.91, 128.39, 128.32, 124.54, 66.27, 44.71, 44.67, 26.21. HRMS (ESI+) m/z calcd for $C_{13}H_{17}O_4N + H^+$ 252.1230, found 252.1228.

1-hydroxy-4,4-dimethyl-1-(3-nitrophenyl)pentan-3-one (4d): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 5.25 – 5.16 (m, 1H), 3.85 (d, *J* = 2.3 Hz, 1H), 2.94 – 2.82 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 216.48, 148.44, 145.35, 131.99, 129.54, 122.57, 120.84, 69.23, 45.22, 44.54, 26.23. HRMS (ESI+) m/z calcd for $C_{13}H_{17}O_4N + Na^+$ 274.1050, found 274.1054.

1-hydroxy-4,4-dimethyl-1-(4-nitrophenyl)pentan-3-one (4e): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.22 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 5.23 (dt, *J* = 8.8, 2.9 Hz 1H), 3.76 (d, *J* = 3.2 Hz, 1H), 2.94-2.80 (m, 2H), 1.15 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 216.54, 150.44, 147.47, 126.60, 123.91, 69.47, 45.24, 44.63, 26.30. HRMS (ESI+) m/z calcd for $C_{13}H_{17}O_4N + Na^+$ 274.1050, found 274.1053.

1-hydroxy-4,4-dimethyl-1-(5-nitrofuran-2-yl)pentan-3-one (4f): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.29 (d, *J* = 3.6 Hz, 1H), 6.58 (d, *J* = 3.5 Hz, 1H), 5.21-5.14 (m, 1H), 3.82 (d, *J* = 5.5 Hz, 1H), 3.16 – 3.03 (m, 2H), 1.17 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 216.25, 159.31, 151.72, 112.78, 109.81, 64.75, 44.70, 41.26, 26.26. HRMS (ESI+) m/z calcd for $C_{11}H_{15}O_5N + NH_4^+$ 259.1288, found 259.1293.

1-hydroxy-4,4-dimethyl-1-(5-nitrothiophen-2-yl)pentan-3-one (4g): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.81 (d, *J* = 4.1 Hz, 1H), 6.88 (d, *J* = 4.1 Hz, 1H), 5.37-5.31 (m, 1H), 3.91 (d, *J* = 4.1 Hz, 1H), 3.05-2.95 (m, 2H), 1.17 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 215.95, 156.10, 128.64, 122.20, 110.13, 66.88, 44.84, 44.64, 26.31. HRMS (ESI+) m/z calcd for $C_{11}H_{15}O_4NS + H^+$ 258.0795, found 258.0794.

1-hydroxy-1-(2-methoxyphenyl)-4,4-dimethylpentan-3-one (4h): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.49 (d, *J* = 7.4 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.38 (d, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.79 (d, *J* = 3.7 Hz, 1H), 3.03 (dd, *J* = 17.4, 2.6 Hz, 1H), 2.76 (dd, *J* = 17.4, 9.0 Hz, 1H), 1.12 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.55, 155.72, 131.32, 128.29, 126.47, 120.90, 110.20, 65.71, 55.32, 44.50, 43.60, 26.12. HRMS (ESI+) m/z calcd for $C_{14}H_{20}O_3 + Na^+$ 259.1305, found 259.1309.

1-(3-(benzyloxy)phenyl)-1-hydroxy-4,4-dimethylpentan-3-one (4i): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.44 (d, *J* = 7.1 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.30-7.22 (m, 1H), 7.03 (s, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.89 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.15-5.03 (m, 1H), 5.09 (s, 2H), 3.56 (d, *J* = 2.8 Hz, 1H), 2.93 – 2.76 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.05, 159.17, 144.92, 137.13, 129.72, 128.73, 128.11, 127.66, 118.36, 114.08, 112.37, 70.15, 70.13, 45.60, 44.55, 26.31. HRMS (ESI+) m/z calcd for $C_{20}H_{24}O_3 + Na^+$ 335.1618, found 335.1631.

1-(4-(benzyloxy)phenyl)-1-hydroxy-4,4-dimethylpentan-3-one (4j): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 5.10 – 5.07 (m, 1H), 5.07 (s, 2H), 3.51 (d, *J* = 2.8 Hz, 1H), 2.86 (d, *J* = 5.8 Hz, 2H), 1.13 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.12, 158.41, 137.12, 135.64, 128.72, 128.09, 127.58, 127.10, 114.99, 70.18, 69.88, 45.55, 44.54, 26.31. HRMS (ESI+) m/z calcd for $C_{20}H_{24}O_3 + Na^+$ 335.1618, found 335.1627.

1-([1,1'-biphenyl]-4-yl)-1-hydroxy-4,4-dimethylpentan-3-one (4k): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.64-7.52 (m, 4H), 7.50-7.39 (m, 4H), 7.35 (t, *J* = 7.2 Hz, 1H), 5.22-5.13 (m, 1H), 3.60 (d, *J* = 2.8 Hz, 1H), 2.97 – 2.85 (m, 2H), 1.16 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.08, 142.20, 140.97, 140.72, 128.92, 127.44, 127.41, 127.24, 126.26, 70.03, 45.57, 44.58, 26.34. HRMS (ESI+) m/z calcd for $C_{19}H_{22}O_2 + Na^+$ 305.1512, found 305.1520.

1-(4-(dimethylamino)phenyl)-1-hydroxy-4,4-dimethylpentan-3-one (4l): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.27 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.07 (d, *J* = 8.7 Hz, 1H), 3.46 (d, *J* = 2.2 Hz, 1H), 2.97 (s, 6H), 2.94 – 2.83 (m, 2H), 1.16 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.05, 150.33, 131.08, 126.74, 112.65, 69.96, 45.50, 44.45, 40.76, 26.27. HRMS (ESI+) m/z calcd for $C_{15}H_{23}NO_2 + H^+$ 250.1802, found 250.1800.

1-(anthracen-9-yl)-1-hydroxy-4,4-dimethylpentan-3-one (4m): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.66 (br, 2H), 8.43 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 2H), 7.55-7.43 (m, 4H), 6.79 (d, *J* = 9.2 Hz, 1H), 3.76 (dd, *J* = 17.8, 10.4 Hz, 1H), 3.57 (s, 1H), 2.93 (d, *J* = 18.1 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 216.93, 134.26, 133.11, 131.86, 129.52, 128.41, 127.38, 125.98, 124.95, 67.03, 44.67, 43.89, 26.37. HRMS (ESI+) m/z calcd for $C_{21}H_{22}O_2$ + Na^+ 329.1512, found 329.1533.

1-(3,4-dimethoxyphenyl)-1-hydroxy-4,4-dimethylpentan-3-one (4n): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.94 (s, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.07 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.57 (d, *J* = 2.1 Hz, 1H), 2.86 (d, *J* = 5.5 Hz, 2H), 1.13 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 217.04, 149.21, 148.56, 135.91, 117.95, 111.17, 109.06, 70.08, 56.07, 56.02, 45.64, 44.52, 26.29. HRMS (ESI+) m/z calcd for $C_{15}H_{22}O_4$ + Na^+ 289.1410, found 289.1413.

2-nitrobenzyl alcohol (5c): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.10 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 4.97 (d, *J* = 6.5 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 147.83, 136.91, 134.28, 130.14, 128.66, 125.17, 62.71. HRMS (ESI+) m/z calcd for $C_7H_7NO_3$ + H^+ 154.0499, found 154.0496.

3-nitrobenzyl alcohol (5d): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.20 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 4.79 (d, *J* = 5.0 Hz, 2H), 2.48 – 2.38 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 148.47, 143.02, 132.76, 129.54, 122.55, 121.57, 64.01. HRMS (ESI+) m/z calcd for $C_7H_7NO_3$ + H^+ 154.0499, found 154.0494.

4-nitrobenzyl alcohol (5e): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.20 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 4.83 (s, 2H), 2.06 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 148.29, 147.44, 127.13, 123.86, 64.14. HRMS (ESI+) m/z calcd for $C_7H_7NO_3$ + H^+ 154.0499, found 154.0494.

2-nitrobenzoic acid (6c): ^{1}H NMR (600 MHz, DMSO) δ (ppm) 13.87 (s, 1H), 7.98 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.86 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.83 – 7.75 (m, 2H). ^{13}C NMR (150 MHz, DMSO) δ (ppm) 165.86, 148.37, 133.08, 132.39, 129.86, 127.24, 123.68. HRMS (ESI+) m/z calcd for $C_7H_5NO_4$ + H^+ 168.0291, found 168.0289.

3-nitrobenzoic acid (6d): ^{1}H NMR (600 MHz, DMSO) δ (ppm) 13.77 (br, 1H), 8.60 (s, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (150 MHz, DMSO) δ (ppm) 165.50, 147.86, 135.32, 132.59, 130.47, 127.23, 123.64. HRMS (ESI+) m/z calcd for $C_7H_5NO_4$ - H^+ 166.0146, found 166.0141.

4-nitrobenzoic acid (6e): ^{1}H NMR (600 MHz, DMSO) δ (ppm) 13.73 (br, 1H), 8.30 (d, *J* = 8.3 Hz, 2H), 8.15 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, DMSO) δ (ppm)

165.80, 149.99, 136.51, 130.66, 123.67. HRMS (ESI+) m/z calcd for $C_7H_5NO_4$ - H^+ 166.0146, found 166.0139.

1-(4-chlorophenyl)-1-hydroxy-4,4-dimethylpentan-3-yl 4-chlorobenzoate (7a): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.02 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.30-7.24 (m, 4H), 5.19 (d, *J* = 10.9 Hz, 1H), 4.51 (d, *J* = 10.1 Hz, 1H), 3.49 (d, *J* = 3.1 Hz, 1H), 1.99-1.82 (m, 2H), 1.01 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 167.15, 142.54, 140.10, 133.10, 131.35, 129.07, 128.63, 128.26, 127.16, 79.55, 69.39, 40.14, 34.81, 26.24. HRMS (ESI+) m/z calcd for $C_{20}H_{22}O_3Cl_2$ + Na^+ 403.0838, found 403.0831.

1-(4-bromophenyl)-1-hydroxy-4,4-dimethylpentan-3-yl 4-bromobenzoate (7b): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.18 (dd, *J* = 11.1, 2.0 Hz, 1H), 4.49 (dt, *J* = 10.3, 3.1 Hz, 1H), 3.46 (d, *J* = 3.7 Hz, 1H), 1.98 – 1.84 (m, 2H), 1.01 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 167.29, 143.04, 132.09, 131.59, 131.47, 128.80, 128.71, 127.53, 121.21, 79.57, 69.46, 40.10, 34.81, 26.24. HRMS (ESI+) m/z calcd for $C_{20}H_{22}O_3Br_2$ + Na^+ 490.9828, found 490.9800.

1-([1,1'-biphenyl]-4-yl)-1-hydroxy-4,4-dimethylpentan-3-yl [1,1'-biphenyl]-4-carboxylate (7k): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.18 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.58-7.52 (m, 4H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.47 – 7.38 (m, 5H), 7.33 (t, *J* = 7.2 Hz, 1H), 5.28 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 10.2 Hz, 1H), 3.56 (d, *J* = 3.0 Hz, 1H), 2.11 – 1.96 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 167.93, 146.30, 143.19, 141.05, 140.40, 140.09, 130.55, 129.13, 128.86, 128.64, 128.41, 127.47, 127.38, 127.32, 127.29, 127.22, 126.26, 79.27, 69.84, 40.20, 34.89, 26.34. HRMS (ESI+) m/z calcd for $C_{32}H_{32}O_3$ + Na^+ 487.2244, found 487.2264.

1-(4-chlorophenyl)-3-hydroxy-4,4-dimethylpentyl 4-chlorobenzoate (8a): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.00 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 6.25 (d, *J* = 10.8 Hz, 1H), 3.36 (dd, *J* = 10.2, 2.7 Hz, 1H), 2.31 (d, *J* = 3.9 Hz, 1H), 2.17 (t, *J* = 13.0 Hz, 1H), 1.77 (t, *J* = 12.7 Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.66, 139.95, 139.65, 133.96, 131.22, 129.02, 128.99, 128.50, 127.75, 75.37, 74.05, 39.64, 34.77, 25.82. HRMS (ESI+) m/z calcd for $C_{20}H_{22}O_3Cl_2$ + Na^+ 403.0838, found 403.0874.

1-(4-bromophenyl)-3-hydroxy-4,4-dimethylpentyl 4-bromobenzoate (8b): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.92 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.28 – 6.14 (m, 1H), 3.35 (dd, *J* = 10.5, 4.1 Hz, 1H), 2.26 (d, *J* = 4.7 Hz, 1H), 2.19 – 2.11 (m, 1H), 1.80 – 1.71 (m, 1H), 0.91 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.79, 140.15, 132.04, 131.95, 131.35, 128.94, 128.65, 128.07, 122.09, 75.37, 74.11, 39.60, 34.77, 25.82. HRMS (ESI+) m/z calcd for $C_{20}H_{22}O_3Br_2$ + Na^+ 490.9828, found 490.9801.

1-(3-(benzyloxy)phenyl)-3-hydroxy-4,4-dimethylpentyl 3-(benzyloxy)benzoate (8i): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.69 (br, 2H), 7.55 – 7.26 (m, 12H), 7.20 (d, *J* = 7.1 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.92 (d, *J* = 7.1 Hz, 1H), 6.26 (d, *J* = 9.7 Hz, 1H), 5.12 (s, 2H), 5.07 (s, 2H), 3.35 (dd, *J* = 9.5, 3.4 Hz, 1H), 2.39 (d, *J* = 4.2 Hz, 1H), 2.22 – 2.09 (m, 1H), 1.86-1.74 (m, 1H), 0.92 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 166.47, 159.15, 158.93, 142.96, 136.99, 136.64, 131.57, 129.87, 129.70, 128.82, 128.74, 128.30, 128.15, 127.73, 127.70, 122.53, 120.44, 118.89, 115.67, 114.16, 113.08, 75.30, 74.36, 70.38, 70.23, 39.95, 34.75, 25.90. HRMS (ESI+) m/z calcd for $C_{34}H_{36}O_5 + Na^+$ 547.2455, found 547.2457.

1-(3,4-dimethoxyphenyl)-3-hydroxy-4,4-dimethylpentyl 3,4-dimethoxybenzoate (8k): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.73 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.03 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.22 (dd, *J* = 10.8, 2.1 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.36 (dd, *J* = 10.3, 3.9 Hz, 1H), 2.54 (d, *J* = 4.6 Hz, 1H), 2.22 – 2.15 (m, 1H), 1.83 – 1.76 (m, 1H), 0.90 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 166.66, 153.38, 149.13, 148.86, 133.99, 123.80, 122.73, 118.57, 112.38, 111.33, 110.42, 110.13, 109.90, 75.36, 74.24, 56.22, 56.14, 56.12, 56.08, 39.88, 34.74, 25.95. HRMS (ESI+) m/z calcd for $C_{24}H_{32}O_7 + Na^+$ 455.2040, found 455.2057.

1-([1,1'-biphenyl]-4-yl)-3-hydroxy-4,4-dimethylpentyl [1,1'-biphenyl]-4-carboxylate (8n): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.19 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.66-7.54 (m, 8H), 7.51-7.39 (m, 5H), 7.35 (t, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 10.6 Hz, 1H), 3.44 (dd, *J* = 10.5, 3.8 Hz, 1H), 2.51 (d, *J* = 4.4 Hz, 1H), 2.25 (t, *J* = 12.7 Hz, 1H), 1.87 (t, *J* = 12.7 Hz, 1H), 0.96 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 166.65, 146.17, 141.09, 140.87, 140.34, 140.10, 130.46, 129.12, 128.92, 128.38, 127.56, 127.51, 127.44, 127.34, 127.28, 126.79, 126.26, 75.35, 74.24, 39.97, 34.78, 25.94. HRMS (ESI+) m/z calcd for $C_{32}H_{32}O_3 + Na^+$ 487.2244, found 487.2259.

ACKNOWLEDGMENTS

This work was supported by NSF grant 1464538 to PGW.

Appendix A. Supplementary Data

Supplementary data to this can be found online at:
https://

We report a systematic study and comparison of the solid-state aldol reactions of solvated and unsolvated lithium pinacolone enolate with a variety of solid aromatic aldehydes. In solution, the reactions are highly-selective for the aldol condensation product at room temperature. Using a mortar and pestle, the reactions with unsolvated lithium pinacolone enolate yielded a mixture of aldol condensation product and aldol addition product at room temperature.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: