N-Tosyl-(S_a)-binam-L-prolinamide as Highly Efficient Bifunctional Organocatalyst for the General Enantioselective Solvent-Free Aldol Reaction

Gabriela Guillena,* Carmen Nájera,* Santiago F. Viózquez

Dpto. Química Orgánica and Instituto de Síntesis Orgánica, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
Fax +34(965)903549; E-mail: gabriela.guillena@ua.es; E-mail: cnajera@ua.es

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Abstract: *N*-Tosyl-(S_a)-binam-L-prolinamide (5 mol%) and benzoic acid (1 mol%) were used as catalysts in the enantioselective direct aldol reaction between different ketones and aldehydes under solvent-free conditions in the presence or absence of water. Under these reaction conditions it was possible to reduce the amount of required ketone to two equivalents to give the corresponding aldol products with high yields, regio-, diastereo- and enantioselectivities. The aldol reaction between aldehydes or the intramolecular aldol reaction can be also performed with excellent results.

Key words: organocatalyzed, aldol reactions, solvent-free, enantioselective, ketone

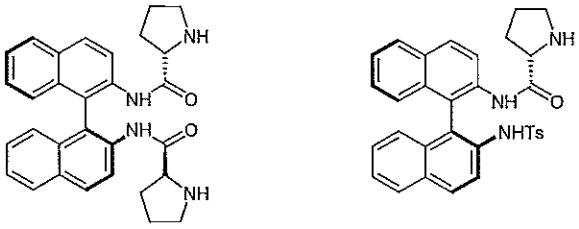

Figure 1 Binam-L-prolinamide-derived catalysts

Bisprolinamides derived from 1,1′-binaphthyl-2,2′-diamine (binam) have been studied as organocatalysts[1] in the aldol reaction[2] under different reaction conditions using alkyl[3] and α-functionalized[4] ketones as source of nucleophile, with recoverable catalyst (S_a)-binam-L-Pro **1** (Figure 1),[3a,c] providing the best results. For this prolinamide, the addition of an equimolecular amount of benzoic acid as co-catalyst in the reaction has been crucial to get a great acceleration in the reaction. Under these reaction conditions, less reactive ketones, such as butanone[3c] and α-functionalized ketones can be used as donors, even in water.[4] Recently, we have described the aldol reaction under solvent-free conditions, reducing the loading of catalyst **1** and the amount of required ketone to two equivalents to give the corresponding products with a high level of selectivity.[5] Mechanistic studies showed that the derived enamines from one or both proline moieties are formed but only one prolinamide works as catalyst. In addition, the presence of benzoic acid as co-catalyst increased the reaction rate but decreased the enantioselectivity.

With these previous results in our hands, we thought that it would be of interest to achieve the replacement of one of the proline residue in catalyst **1**, by an acidic moiety such as a sulfonamide group, which might allow the reduction of the amount of acid co-catalyst. In addition, the sulfonamide moiety can activate the carbonyl group of the acceptor aldehydes through a hydrogen bond acting as a bifunctional catalyst. Here, we report the application of the unsymmetrical (S_a)-binam-L-prolinamide sulfonamide derivative **2**[6] (Figure 1) in the aldol reaction under solvent-free reaction conditions.[7]

Catalyst **2** was prepared by a modified procedure of the standard method[6] using *p*-toluenesulfonyl chloride and commercially available (*S*)-1,1′-binaphthyl-2,2′-diamine [(S_a)-binam], and subsequently coupling with the in situ generated Fmoc-L-Pro chloride followed by deprotection with piperidine, giving compound **2** in 80% overall yield after purification.

Then, catalyst **2** was tested in the reaction between cyclohexanone and 4-nitrobenzaldehyde under solvent-free conditions, to optimize the reaction conditions. The addition of a small amount of benzoic acid (1 mol%) was required to obtained the aldol product **4aa** in shorter reaction times (Table 1, compare entries 1 and 2). Under the same reaction conditions, catalysts **1** showed to be less efficient, giving after three hours, 90% of conversion, with the aldol products being obtained with a slightly lower diastereo- and enantioselectivity (Table 1, entry 3). In some organocatalyzed aldol reactions, the addition of water to an organic solvent has shown to have a positive effect on the reaction rates.[8] Thus, the effect of the use of some amount of water in the reaction catalyzed by **2** was studied (Table 1). First, the addition of 1 mL of water was evaluated. Under these conditions, the reaction was much slower, giving the aldol product **3aa** with lower conversion, diastereo- and enantioselectivity (Table 1, compare entries 2 and 4). Decreasing gradually the amount of added water, caused an acceleration in the reaction rate as well as an increase in the conversion, diastereo- and enantioselectivity ~~was achieved~~ (Table 1, entries 5–7), with the best results being obtained by adding only 33 μL (7 equiv) of water to the reaction mixture (Table 1, entry 7). This effect was in contrast to that observed when proline was used as catalyst for the aldol reaction under solvent-free-conditions, in which the addition of small amounts of wa-

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Table 1 Effect of the Addition of Water in the Reaction between 4-Nitrobenzaldehyde and Cyclohexanone under Solvent-Free Conditions[a]

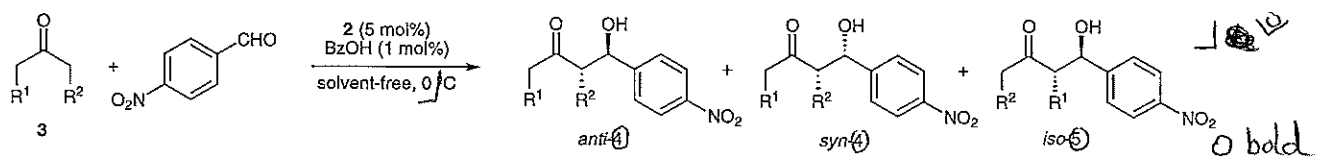
Entry	H_2O (μL)	T (°C)	Time (h)	Conversion (%)[c]	*anti*/*syn*[d]	ee (%)[e]
1[b]	–	0	12	97	97:3	99
2	–	0	6	99	99:1	97
3[f]	–	0	3	90	96:4	94
4	1000	0	26	44	86:16	94
5	500	0	23	39	93:7	96
6	125	0	18	70	86:11	98
7	33	0	4	99	99:1	98
8[f]	33	0	3	97	97:3	92

[a] Reaction conditions: 4-nitrobenzaldehyde (0.25 mmol), cyclohexanone (2 equiv), **2** (5 mol%), BzOH (1 mol%), 0 °C, unless stated otherwise.
[b] The reaction was carried out in the absence of BzOH.
[c] Conversion based on the unreacted aldehyde.
[d] Determined by ^{1}H NMR of the crude product.
[e] Determined by chiral-phase HPLC analysis for the *anti* isomer.
[f] Reaction conditions: catalyst **1** (5 mol%), BzOH (1 mol%).

ter caused a decrease in the reaction rate.[7c] Applying these reaction conditions using catalyst **1** (5 mol%), benzoic acid (1 mol%), the achieved result in terms of conversion, diastereo- and enantioselectivity were poorer than those obtained using catalyst **2** (Table 1, compare entries 7 and 8) where longer reaction time was required.

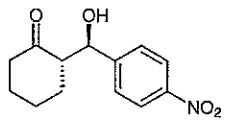
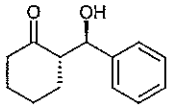
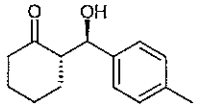
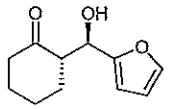
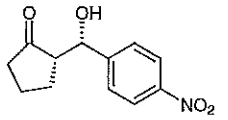
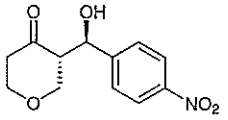
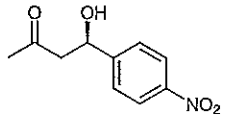
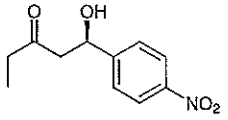
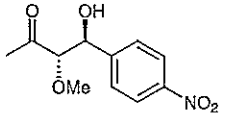
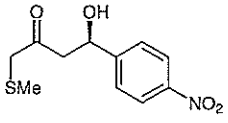
The scope of catalyst **2** under anhydrous and wet solvent-free reaction conditions was studied using several aromatic aldehydes and cyclic, acyclic and α-functionalized ketones (Scheme 1 and Table 2). For cyclic ketones the reaction proceeded smoothly in all cases giving mainly the *anti* isomers **4** (Table 2, entries 1–8), except for cyclopentanone, with isomer *syn*-**4ba** being in this case the major isomer (Table 2, entries 9 and 10). The reaction times were shorter under wet than under anhydrous conditions. Whereas 4-nitrobenzaldehyde gave the corresponding aldol product in a short reaction time, nonactivated aldehydes such as benzaldehyde or tolualdehyde needed longer reaction time to give the aldol product in moderated yields (36–76%) but in excellent diastereo- and enantioselectivities (96% de and 96% ee; Table 2, entries 3–6). Also heteroaromatic aldehydes such as furfural were suitable donor for this process yielding mainly *anti*-**4ad** in better yield (52%) under wet than under anhydrous conditions and in high diastereo- and enantioselectivity (Table 2, entries 7 and 8). Cyclopentanone gave mainly aldol *syn*-**4ba** with slightly better diastereo- and enantioselectivity under anhydrous than under wet conditions (Table 2, entries 9 and 10). Surprisingly, 4-pyranone,[9] gave the expected *anti* isomer (major isomer) in only 50% yield under wet conditions compared to 93% yield obtained under anhydrous conditions, with comparable diastereo- and enantioselectivities achieved for both cases (Table 2, entries 11 and 12). When acetone was allowed to react with 4-nitrobenzaldehyde the aldol **4da** was obtained in good yield and enantioselectivity in only 16 hours under wet conditions, whereas 48 hours were required under anhydrous conditions (Table 2, entries 13 and 14). Longer reaction times were required with less reactive 2-butanone giving mainly the *iso* isomer **5ea** with excellent enantioselectivity under wet conditions (Table 2, entries 15 and 16).

In all cases, with the exception of 2-butanone, the achieved diastereo- and enantioselectivities were better than those previously obtained using catalyst **1** (5 mol%) and benzoic acid (10 mol%) under solvent-free conditions, with longer reaction times being required with catalyst **2**.[5] Finally, several α-functionalized ketones were reacted with 4-nitrobenzaldehyde under wet and anhydrous solvent-free conditions. Whereas α-methoxyacetone gave mainly the *anti* isomer **4fa** in shorter reaction time under anhydrous conditions (Table 2, entries 17 and 18), α-methylsulfanylacetone gave as main product *iso*-**5ga** with good enantioselectivity, with catalyst **2** (10 mol%) and benzoic acid (5 mol%) being needed to obtain 87% yield under anhydrous conditions (Table 2, entries 19 and 20).

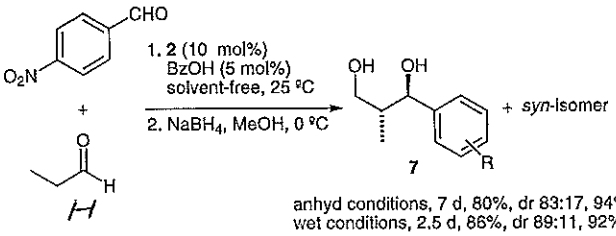


Scheme 1 Reaction between 4-nitrobenzaldehyde and different ketones under solvent-free conditions

Table 2 Reaction of Aldehydes with Cyclohexanone under Anhydrous and Wet Solvent-Free Conditions[a]

Entry	Major product	Time (h)	Yield (%)[b]	4/5	*anti*/*syn*[c]	ee (%)[d]
1		6	94	–	99:1	98
2[e]		4	98	–	99:1	98
	anti-**4aa**					
3		120	76			
4[e]		72	74	–	99:1	98
	anti-**4ab**					
5		120	36	–	98:2	96
6[e]		91	52	–	>99:1	98
	anti-**4ac**					
7		26	27	–	96:4	92
8[e]		91	52	–	97:3	94
	anti-**4ad**					
9		15	90	–	32:68	84
10[e]		7.5	88	–	37:63	78
	syn-**4ba**					
11		24	93	–	97:3	89
12[e]		19	50	–	98:2	94
	anti-**4ca**					
13		48	86	–	–	84
14[e]		16	88	–	–	86
	~~*anti*-**4da**~~					
15		96	62	23:77	>99:1	90
16[e]		68	81	36:64	>99:1	98
	iso-**5ea**					
17		48	73	78:22	82:18	93
18[e]		65	76	72:28	84:16	94
	anti-**4fa**					
19[f]		120	87	17:83	>99:1	88
20[e,f]		67	40	19:81	>99:1	86
	iso-**5ga**					

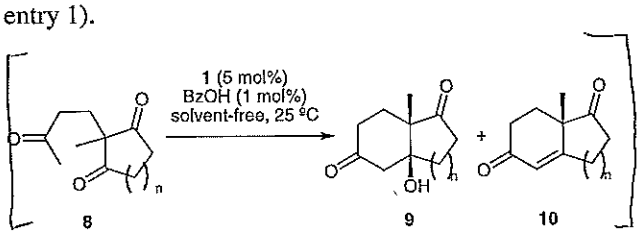
[a] Reaction conditions: 4-nitrobenzaldehyde (0.25 mmol), ketone (2 equiv), **2** (5 mol%), BzOH (1 mol%), 0 °C, unless stated otherwise.
[b] Yield after purification by column chromatography.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis for the major isomer.
[e] H_2O (33 μL) was added to the reaction mixture.
[f] Catalyst **2** (10 mol%) and BzOH (5 mol%) were used.



Scheme 2 Reaction between 4-nitrobenzaldehyde and propanal under solvent-free conditions

Aldehydes can also act as donors in this transformation. In this case catalyst **2** (10 mol%) and benzoic acid (5 mol%) have to be used at 25 °C to perform the reaction. When propanal (5 equiv) and 4-nitrobenzaldehyde were allowed to react under these conditions 1,3-diol **7** was obtained under anhydrous conditions in seven days with 80% yield, 66% de and 94% ee, after in situ reduction of the corresponding aldol with $NaBH_4$ in MeOH (Scheme 2). When the same reaction was carried out by adding 33 µL of water (wet conditions), compound **7** was obtained after 2.5 days with 86% yield, 78 de and 92% ee (Scheme 2). These results are superior in terms of reaction time, yield, diastereo- and enantioselectivity to those reported previously using catalyst **1** (5 mol%) and benzoic acid (10 mol%).[5b] In this case six days of reaction time was required to yield 45% of compound **7** with 56% de and 85% ee after final reduction.

Finally, these 2.5 days of reaction time and wet solvent free-conditions were applied to the intramolecular aldol reaction (Robinson-type annulation),[10] which has been extensively used in the synthesis of natural products (Scheme 3 and Table 3).[1o,2] Using catalyst **2** (5 mol%) and benzoic acid (1 mol%) at room temperature under anhydrous solvent-free conditions the 6-(enolendo)-*exo*,*trig* cyclization of triketone **8a** (n = 2), led directly to the corresponding Wieland–Miescher ketone[11] **9a** in only 27 hours with excellent yield and enantioselectivity (Table 3, entry 1).



Scheme 3 Intramolecular aldol reaction under solvent-free conditions

A shorter reaction time was required when a small amount of water (14 µL, 3 equiv) was added to the reaction mixture (wet conditions), giving ketone **9a** with similar yield and ee (Table 3, entry 2). These results are better when compared to those reported in the literature using MeCN as solvent in the presence of $HClO_4$ and 50 mol% of L-proline at 80 °C,[10c] affording compound **9a** in 73% yield and 71% ee. The synthesis of bicyclic compound **9b**, which is an important intermediate in the total synthesis of steroids was optimized using L-proline (3 mol%) in DMF as solvent at room temperature.[10d] Under these conditions product **10a** (n = 1) was obtained with 100% yield and 93% ee, with a subsequent dehydration step being necessary to achieve the desired product. Under solvent-free conditions and using catalyst **2**, the main product observed was the indanone derivative **9b**. After column chromatography purification, the only product isolated with similar yield, under both anhydrous and wet conditions, was compound **9b**, with better enantioselectivity obtained under wet conditions (Table 3, entries 3 and 4).

Table 3 Intramolecular Aldol Reaction under Anhydrous and Wet Solvent-Free Conditions[a]

Entry	Product	n	Time (h)	Yield (%)[b]	9/10[c]	ee (%)[d]
1	**9a**	2	27	95	100:0	90
2[e]	**9a**	2	16	90	100:0	88
3	**9b**	1	48	84	67:36	83
4[e]	**9b**	1	48	85	70:30	90

[a] Reaction conditions: triketone **8** (0.25 mmol), **2** (5 mol%), BzOH (1 mol%), 25 °C.
[b] Yield after purification by column chromatography for compound **9**.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis of the isolated product.
[e] H_2O (14 µL, 3 equiv) was added to the reaction mixture.

In conclusion, sulfonamide **2** in the presence of a small amount of benzoic acid has shown to be a useful catalyst to perform the intramolecular and the ketone–aldehyde or aldehyde–aldehyde intermolecular aldol reaction under solvent-free conditions.[12] The aldol products were obtained with good yields and excellent diastereo- and enantioselectivities, generally, with the addition of a small amount of water (3–7 equiv) to the reaction mixture leading to an increase in the reaction rates. In general, these results are superior in terms of diastereo- and enantioselectivities to those previously reported using L-proline or prolinamide **1** as catalyst under solvent-free conditions. Further scope and application of sulfonamide catalyst **2** in this and other related transformations are currently being studied.

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References and Notes

(1) For comprehensive books and selected reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **2005**. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Kočovský, P.; Malkov, A. V. *Tetrahedron* **2006**, *62*, 255. (e) Lelais, G.; McMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (f) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (g) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465. (h) List, B. *Chem. Commun.* **2006**, 819. (i) Gaunt, M. J.; Johansonn, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (j) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (k) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**. (l) List, B. *Chem. Rev.* **2007**, *107*, 5413. (m) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (n) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (o) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. (p) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493. (q) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757.

(2) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249.

(3) (a) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 729. (b) Gryko, D.; Kowalczyk, B.; Zawadzki, L. *Synlett* **2006**, 1059. (c) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493. (d) *Corrigendum*: Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1031. (e) Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754. (f) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197. (g) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247.

(4) (a) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027. (b) *Corrigendum*: Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1030. (c) Guillena, G.; Hita, M. C.; Nájera, C. *Arkivoc* **2007**, (iv), 260. (d) *Corrigendum*: Guillena, G.; Hita, M. C.; Nájera, C. *Arkivoc* **2007**, *(i)*, 146. (e) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1272.

(5) (a) Guillena, G.; Hita, M. C.; Nájera, C.; Viózquez, S. F. *Tetrahedron: Asymmetry* **2007**, *18*, 2300. (b) Guillena, G.; Hita, M. C.; Nájera, C.; Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933.

(6) Chen, T.; Gao, J.; Shi, M. *Tetrahedron* **2006**, *62*, 6289.

(7) For some other organacatalyzed enantioselective aldol reactions under solvent-free conditions, see: (a) Rodríguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 6924. (b) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957. (c) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 4710.

(8) Nyberg, A. I.; Usano, A.; Pinko, P. M. *Synlett* **2004**, 1891.

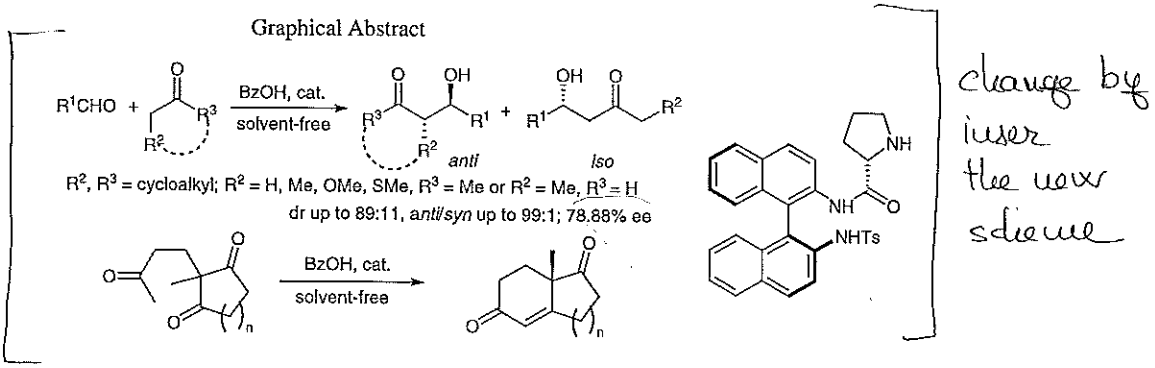
(9) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198.

(10) (a) Eder, U.; Wiechert, R.; Sauer, G. Ger. Patent, DE 2014757, **1971**; *Chem. Abstr.* **1972**, *76*, 14180. (b) Hajos, Z. G.; Parrish, D. R. Ger. Patent, DE 2102623, **1971**; *Chem. Abstr.* **1972**, *76*, 59072. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (e) Hajos, Z. G.; Parrish, D. R. In *Org. Synth., Coll. Vol. VII*; Freeman, J. P., Ed.; Wiley: New York, **1990**, 363. (f) Buchschacher, P.; Fürst, A.; Gutzwiller, J. In *Org. Synth., Coll. Vol. VII*; Freeman, J. P., Ed.; Wiley: New York, **1990**, 368. (g) Kwiatkowski, S.; Syed, A.; Brock, C. P.; Watt, D. S. *Synthesis* **1989**, 818. (h) Tietze, L. F.; Utecht, J. *Synthesis* **1993**, 927.

(11) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.

(12) **Representative Experimental Procedure:**
Anhydrous Solvent-Free Conditions: To a mixture of the corresponding aldehyde (0.25 mmol), catalyst **2** (0.0125 mmol, 6.5 mg) and benzoic acid (0.0025 mmol, 0.3 mg) at 0 °C was added the corresponding ketone (0.5 mmol). The reaction was stirred until the aldehyde was consumed (monitored by TLC). Then, the crude product was diluted in CH_2Cl_2 (10 mL), silica gel was added and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (hexanes–EtOAc) to yield the pure aldol product.
Wet Solvent-Free Conditions: To a mixture of the corresponding aldehyde (0.25 mmol), catalyst **2** (0.0125 mmol, 6.5 mg), benzoic acid (0.0025 mmol, 0.3 mg), H_2O (33 μL) was added at 0 °C followed by the corresponding ketone (0.5 mmol). The reaction was stirred until the aldehyde was consumed. The crude product was diluted in CH_2Cl_2 (10 mL), $MgSO_4$ was added and filtered. To the filtrate, silica gel was added and the above purification procedure was followed to obtain the aldol product.

Graphical Abstract



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