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COMMUNICATION

Practical access to highly enantioenriched quaternary carbon Michael adducts using simple organocatalysts†

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A three component catalyst system entailing an amino acid (O^{t}Bu-L-threonine), a hydrogen bond donor (sulfamide), and an amine base (DMAP) allows α-branched aldehyde addition to nitroalkenes in good to high yield and excellent ee. Importantly, the lowest reported catalyst loading (5.0 mol%) and aldehyde stoichiometry (1.2–2.0 equiv) is demonstrated and in most instances the best current product profile is observed.

Natural product and pharmaceutical drug synthesis present multiple levels of challenge and complication that must be concurrently overcome. Beyond the chosen synthetic strategy, a simplistic view holds that construction of the carbon backbone and functional group manipulation are the basic tasks. In this context methods allowing carbon–carbon bond forming reactions under mild conditions are of interest and especially so when they address the long standing problem of stereogenic quaternary carbon bond formation.[1,2] The Michael reaction affords this possibility when employing α,α′-substituted aldehydes, and the resulting products would be considered high value multifunctional building blocks for natural product elaboration.

Organocatalysts requiring synthesis are common and reports on their facilitation of *unbranched* aldehyde, *e.g.* 2–3 equiv of *n*-pentanal, addition to β-nitrostyrene in the presence of 1–5 mol% of a proline derivative allow product formation in excellent yield, *dr*, and *ee*.[3] However, these low catalyst loadings are not sustainable when *branched* (α,α- or α,α′-substituted) aldehydes are examined.[4] Investigations detailing the use of multiple α,α-substituted and α,α′-substituted aldehydes are uncommon and have waned since the thorough reports of Barbas,[5] Jacobsen,[6] and Connon.[7] These reports and others highlight the continuing challenge associated with quaternary carbon bond formation, and expound the use of 10 mol%,[8,9] 20 mol%,[10,11] or 30 mol%[12] organocatalyst loading to add isobutyraldehyde (minimum of 2.0 equiv)[13] to 2-substituted-nitroethenes. Hence, advances have been made, but room for improvement remains regarding catalyst loading, aldehyde stoichiometry, substrate scope, and reaction time.

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† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for compounds, and copies of ^{1}H NMR spectra and HPLC data. See DOI: 10.1039/c0ob00822b

Two bodies of unrelated literature piqued our interest in the Michael reaction. The first is recent, constituting amino acid catalyzed Michael reactions in the presence of a base,[10a,d,f,14,15] while the other has been studied for decades and details the now well understood self-assembly of carboxylate anions with hydrogen bond donors, *e.g.* amino acids with ureas or thioureas.[16] Our open question was whether the self-assembly of a hydrogen bond donor to the carboxylate of an amino acid would facilitate cooperative bifunctional organocatalysis, and thereby constructively impact stereoselectivity, reaction rate, and/or substrate breadth. In this light, we demonstrate here what we believe is the first synergistic use of an amino acid, a hydrogen bond donor, and a base for an organocatalytic reaction. Importantly, each catalyst component is commercially available.

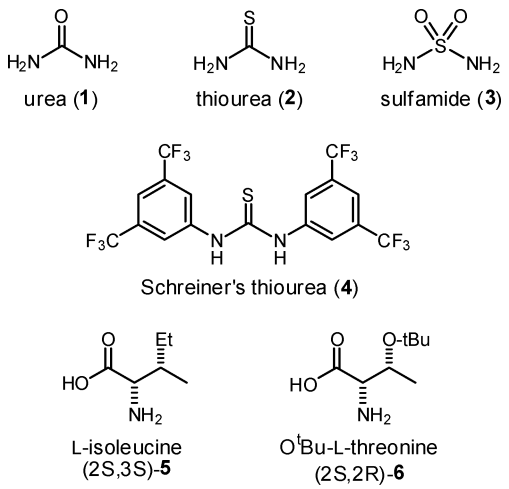
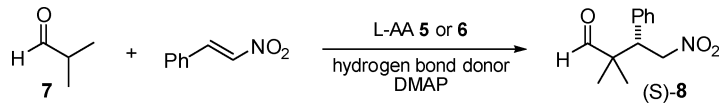


Fig. 1 Hydrogen bond donors and amino acids of interest.

Amino acids are well-known to favor their zwitterionic form. In this context addition of a base, to free the primary amine for catalysis, made sense. Our proof of concept succeeded when we combined isoleucine, Et_3N, and urea (**1**, Fig. 1) in the presence of isobutyraldehyde and β- nitrostyrene (Table 1, entry 1).[17] The reaction was further optimized (Table 1) by examining a large number of amino acid, hydrogen bond donor, and base combinations (see ESI for a complete list†).[18,19] Entries 3, 6, 8, 9, and 12 (Table 1) are of particular interest and five salient points follow. (1) The lowest aldehyde-to-β-nitrostyrene (1.2 : 1.0) ratio is used (entries 4, 6, 9).[13] (2) The lowest catalyst loading

Table 1 Optimization of isobutyraldehyde addition to β-nitrostyrene (see Fig. 1 for catalyst components)[a]



Entry	**7** (equiv)	L-AA **5** or **6**/mol (%)	H-bond donor/mol (%)	DMAP (mol%)	Time/h	Yield (%)[b]	ee (%)[c]
1	2	isoLeu/10	Urea **1**/10	10[d]	24	53	90
2	2	isoLeu/5	Sulfamide **3**/5	5	24	65	97
3	2	O^{t}Bu-Thr/2	Thiourea **4**/2	8	5	82	93
4	1.2	O^{t}Bu-Thr/2	Thiourea **4**/2	8	5	65	91
5	2	O^{t}Bu-Thr/5	Thiourea **4**/5	5	2	99	94
6	1.2	O^{t}Bu-Thr/5	Thiourea **4**/5	5	3	99	93
7	2	O^{t}Bu-Thr/3	Sulfamide **3**/3	3	24	86	97
8	2	O^{t}Bu-Thr/5	Sulfamide **3**/5	5	4	99	98
9	**1.2**	**O^{t}Bu-Thr/5**	**Sulfamide 3/5**	**5**	**7**	**97**	**98**
10	1.2	O^{t}Bu-Thr/5	—	5	7	~5[e]	—
11	1.2	O^{t}Bu-Thr/5	Sulfamide **3**/5	—	7	~0[e]	—
12	2	O^{t}Bu-Thr (Li salt)/5	Sulfamide **3**/5	—[f]	5	99	95
13	2	O^{t}Bu-Thr (Li salt)/5	—	—[f]	24	92	88

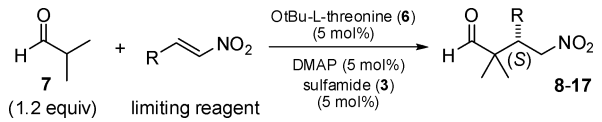
[a] 25 °C, toluene (1.0 M), except entries 3–6: cyclohexane (1.0 M) is optimal. [b] Isolated yield data. [c] HPLC data (Chiralcel OD-H column). [d] Et_3N was used instead of DMAP. [e] HPLC area % data. [f] Preformed lithium salt of O^{t}Bu-L-threonine (5 mol%) used, no DMAP added.

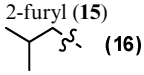
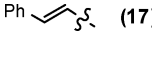
(O^{t}Bu-L-threonine, 2 mol%) to date was demonstrated (entries 3 & 4). (3) High yield and enantioselectivity are coupled with short reaction times (3–7 h).[4,8–12,15] (4) The active organocatalyst is extraordinary because it requires no synthesis, requiring only the addition of commercially available compounds (Fig. 1). Finally, (5) to our knowledge this is the first demonstration of the utility of the most simple sulfamide (Fig. 1, **3**) as a hydrogen bond donor in the field of organocatalysis.

Although thiourea **4**[20] allowed a 2.0 mol% catalyst loading it consistently provided lower enantioinduction than **3** (5 mol%), see Table 1 (entries 3 & 4 *vs.* 8 & 9). Consequently, we used the sulfamide (**3**) hydrogen bond donor for the remainder of our study. It is important to note that removal of one of the three catalyst components results in reaction failure (Table 1, entries 9–11). Interestingly, the lithium salt of O^{t}Bu-L-threonine enabled the reaction to occur without the presence of a hydrogen bond donor (Table 1, entry 13), but required greater quantities of the aldehyde (2.0 equiv *vs.* 1.2 equiv), provided notably lower *ee* (88 *vs.* 98), and drastically longer reaction time (24 *vs.* 7 h). These limitations made the lithium salt, alone, impracticable for the more challenging substrates shortly discussed. Furthermore, when using the optimized reaction conditions (Table 1, entry 9) replacing sulfamide (**3**) by urea (**1**) or thiourea (**2**) resulted in much slower reactions and moderate product *ee* (80%) for both. Finally, *n*-heptane can be used instead of toluene without detriment.

A current theme within organocatalysis is to meet the stoichiometry requirements governing practical organic synthesis. In this vein, we reacted a range of electron deficient and rich aryl substituted β-nitrostyrenes with only 1.2 equiv of isobutyraldehyde (Table 2, entries 1–8).[13] In all instances, except one (Table 2, entry 7), excellent isolated yields 85–98% and *ees* ≥96% were found within 24 h. Of particular note, 2-isobutyl-nitroethene and 2-styryl-nitroethene were examined to highlight the electronic, steric, and functional group diversity the method can afford. Again using 1.2 equiv of isobutyraldehyde, both substrates provided excellent product profiles (Table 2, entries 9 and 10), in fact the best currently known.[7,10d] The method is of further value

Table 2 Isobutyraldehyde addition to 2-substituted-nitroethenes[a]



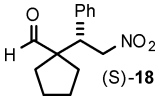
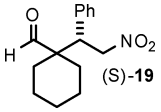
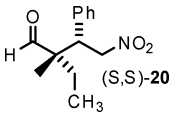
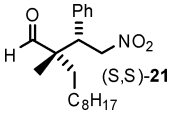
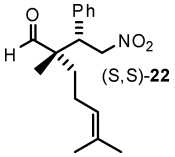
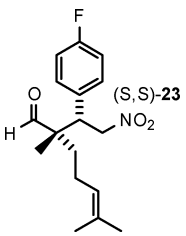
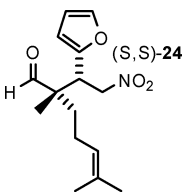
Entry	Product, R =	Time/h	Yield (%)[b]	*ee* (%)[c]
1	C_6H_5 (**8**)	7	97	98
2	*p*-ClC_6H_4 (**9**)	24	98	96
3	*p*-FC_6H_4 (**10**)	24	93	98
4	*o*-BrC_6H_4 (**11**)	24	88	96
5	*p*-MeC_6H_4 (**12**)	24	85[d]	99
6	*p*-$MeOC_6H_4$ (**13**)	24	90[d]	98
7	*o*-$MeOC_6H_4$ (**14**)	36	72[d]	96
8	2-furyl (**15**)	8	98	98
9[e]	 (**16**)	36	70[d]	96
10[e]	 (**17**)	6	98	97

[a] 25 °C, toluene (1.0 M). [b] Isolated yield data after water work-up followed by high vacuum drying, see ESI data for proof of purity (^{1}H NMR and HPLC).† [c] HPLC data. [d] Required chromatography.

because several products (Table 2, entries 1–4, 8, and 10) could be isolated in high chemical purity (>96%, ^{1}H NMR and HPLC) after a simple water work-up and high vacuum drying. This was possible because these reactions, in general, are by-product free, the β-nitrostyrene was fully consumed, the small excess of volatile isobutyraldhyde was readily removed under high vacuum drying, and the amino acid, DMAP, sulfamide catalyst system is water soluble on work-up.

Cyclopentane- and cyclohexanecarboxaldehydes are more sterically congested and infrequently examined. For cyclopentanecarboxaldehyde,[5,7,10b,d,e,21] we achieved the top result to date concerning starting material ratio (2 : 1), catalyst loading (5 mol%), and product profile (Table 3, entry 1). We then turned our attention to cyclohexanecarboxaldehyde

Table 3 Various aldehyde additions to 2-substituted-nitroethenes[a]

Entry	Product	t/h	Yield (%)[b]	*dr*[c]	*ee* (%)[c]
1	 (S)-**18**	7	89	—	97
2		30	64	—	90
3[d]	(S)-**19**	48	88	—	91
4	 (S,S)-**20**	12	84	70 : 30	97
5	 (S,S)-**21**	12	71	78 : 22	91
6	 (S,S)-**22**	12	70	77 : 23	98
7	 (S,S)-**23**	36	80	77 : 23	99
8	 (S,S)-**24**	16	83	76 : 24	97

[a] Reaction conditions: aldehyde/nitroalkene (2 : 1), O^{t}Bu-L-threonine (**6**) (5 mol%), sulfamide (**3**) (5 mol%), DMAP (15 mol%) in toluene (1.0 M) at 25 °C. [b] Isolated yield data after chromatography. [c] HPLC analysis. [d] O^{t}Bu-L-threonine (**6**) (10 mol%), sulfamide (**3**) (10 mol%), DMAP (10 mol%) in toluene (1.0 M) at 25 °C.

which is inexpensive compared to cyclopentanecarboxaldehyde, but essentially not reported on.[22,23] The best previous *ee* was 64%,[23] and using our standard 5 mol% catalyst loading with a cyclohexanecarboxaldehyde/β-nitrostyrene ratio of 2 : 1, we isolated compound (*S*)-**19** in 64% yield with the greatly increased *ee* of 90% within 30 h. When the catalyst loading was increased to 10 mol% the yield increased to 88% (Table 3, entries 2 and 3).

Aldehydes with nonequivalent α-substituents (α,α′-substituted aldehydes) provide Michael products containing stereogenic quaternary carbons and these products were obtained in good yield and excellent *ee*, but with moderate diastereomeric ratios (Table 3, entries 4–8). The diastereomeric ratios are likely a reflection of the (*E*)- to (*Z*)-enamine ratios of the *in situ* formed enamine. This is supported by the fact that our *drs* broadly match those reported in the literature for the same (**20–22**) or similar products (**23** and **24**) when using unrelated organocatalysts.[5–7]

Catalyst self-assembly as a strategy for organocatalytic Michael reactions with β-nitrostyrene is known,[15,24] but only Demir has examined quaternary carbon bond formation.[25–27] Evidence for catalyst self-assembly in our system is based on precedent and preliminary evidence. For example, it is well established that hydrogen bond donors strongly bind to amino acid carboxylate anions having ammonium counter ions.[16] It is therefore a reasonable and strong possibility that sulfamide (**3**) binds to the carboxylate anion of O^{t}Bu-L-threonine having a protonated DMAP counter ion (Fig. 2).[28] Furthermore, decreasing the amount of DMAP or sulfamide, relative to the optimal 1 : 1 : 1 ratio with O^{t}Bu-L-threonine, results in a non-linear decrease in the reaction rate. Moderate increases in the amount of DMAP or sulfamide, relative to the optimal 1 : 1 : 1 ratio with O^{t}Bu-L-threonine, have little effect on the reaction; but addition of larger quantities of DMAP (15 mol% *vs.* 5 mol%) results in reaction rate acceleration (Table 3, see reaction conditions). This base effect has been previously described by Yan.[10c] Finally, the lack of solubility of O^{t}Bu-L-threonine and sulfamide, until all three catalyst components are present, is another indicator that self-assembly is occurring. With this background, a preliminary mechanism is proposed.

The presence of a thiourea moiety in a bifunctional Michael organocatalyst is associated with the orbital activation of a nitroalkene and the simultaneous forced proximity (pre-transition organization) of the nitroalkene with the enamine.[6,29] Here it is reasonable to assume, after self-assembly has occurred, that a similar scenario unfolds; albeit with sulfamide (**3**) strongly associating with the carboxylate anion and simultaneously hydrogen bonding with the nitroalkene (Fig. 2, synclinal I).[30–32]

Why sulfamide (**3**), and not simple urea (**1**) or thiourea (**2**), Fig. 1, is more effective can be rationalized by invoking the distorted tetrahedral geometry at the sulfur atom of **3**. This allows one of the oxygens of sulfamide to always be in a position to take part in an electrostatic interaction with the protonated nitrogen atom of DMAP. If occurring, the carboxylate, protonated DMAP, sulfamide aggregate would represent a closed, or cyclic, assembly of the three interacting partners as depicted in Fig. 2. This configuration would be expected to be more rigid and populated than the corresponding 'open acyclic systems' based on urea (**1**) or thiourea (**2**), leading to increased levels of stereoinduction and increased reaction rate.

When a lithium counter ion is present and no hydrogen bond donor is present (Table 1, entry 13), the basic model would still be valid, but now the nitro group would be directly associated with the lithium cation. To overcome the shortened interaction distance (no hydrogen bond donor intermediary), a synperiplanar transition state (not shown) would be required. In this situation, increased substituent eclipsing effects would raise the transition state energy, slowing down the reaction and possibly allowing the non-productive steric pathway (Fig. 2, synclinal IV) to compete. These after the fact explanations account for the much slower reaction time and lower *ee* in the absence of a hydrogen bond donor (Table 1, compare entries 9 and 13).

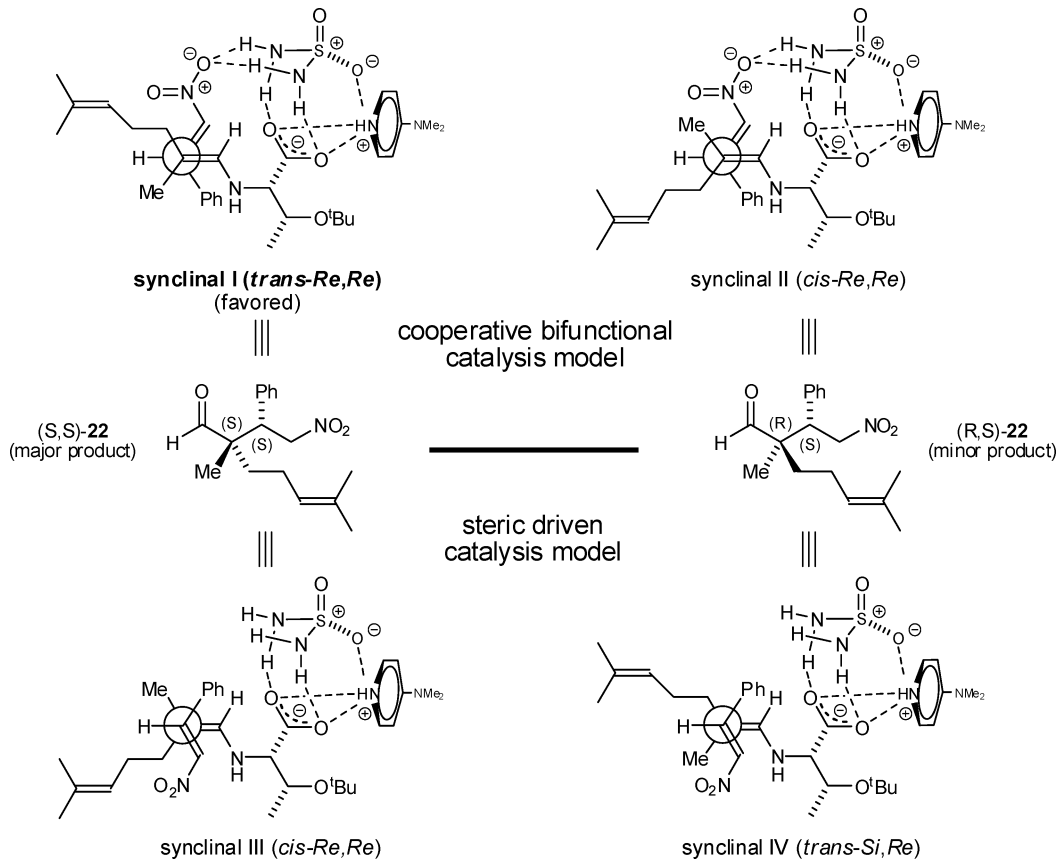


Fig. 2 Postulated transition states for α,α′-substituted aldehyde addition to β-nitrostyrene (Table 3, entry 6 modelled).

A synclinal Newman transition state model rationalizes the stereochemical outcome of enamine additions to nitroalkenes, as elaborated on in the work of Risaliti[33] and Seebach;[34] and, more recently, for the amino acid catalyzed version, by Yoshida.[10a,f] With these points in mind, we sought to explain the observed absolute and relative stereochemistry of our products (**8**–**24**). For this purpose, we used an α,α′-substituted aldehyde for our transition state model: 2,6-dimethylhept-5-enal (Table 3, entry 6). The major product is (*S*,*S*)-**22**, based on chiral HPLC, ^{1}H NMR spectroscopic data, and comparison of these data with the published values.[5,6] In the proposed transition states (Fig. 2), the L-threonine backbone of the enamine minimizes steric interactions *via gauche* staggering, which projects the carboxylate moiety to the α-face of the enamine. A reasonable assumption is that the (*E*)-enamine prevails, in this scenario the synclinal I facial approach accounts for the enantio- and diastereocontrol observed in the major product (*S*,*S*)-**22** (Fig. 2) and consequently for all other products shown here. The minor product, (*R*,*S*)-**22**, is explainable based on the (*Z*)-enamine (synclinal II, Fig. 2). A steric based model (synclinal III, no H-bonding assistance) can also explain the stereochemical outcome for the major product (*S*,*S*)-**22** (Fig. 2). However, it requires the minor (*Z*)-enamine, and thereby fails to explain how the *major* product would be formed.

In summary, quaternary carbon–carbon bond formation in these Michael reactions entails cooperative bifunctional catalysis (synclinal I and II, Fig. 2). The amino acid's primary amine transforms the aldehyde into an enamine, while the second functional group, here the carboxylate-sulfamide assembly, activates the nitroalkene and directs it into bonding distance proximity of the β-carbon of the enamine *via* hydrogen bonding. The carboxylate-sulfamide assembly may also increase the rate of enamine formation by enforcing a conformational preference in the amino acid backbone. These combined facets may account for the low catalyst loading and need for only a small excess of the aldehyde as reported here.

In closing, we have developed a new catalyst assembly based approach for the catalytic enantioselective formation of an important class of Michael products bearing quaternary carbons. Through the hitherto unknown synergistic combination of an amino acid, a base, and a hydrogen bond donor, it is now possible to promote these reactions with lower loadings of both the catalyst and the aldehyde than previously feasible, and within relatively short reaction times. The cooperation of the three catalyst components, and their inherently tunable nature, may open up new avenues for the pursuit of organocatalytic reactions in general.[19] Preliminary modelling suggests that other Michael acceptors (*e.g.* maleimide, DEAD, unsaturated sulfones, *etc.*), the Mannich reaction, and mechanistically related reactions, will be amenable to this approach.

Acknowledgements

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Notes and references

1 *The Way of Synthesis*T. Hudlický and J. W. Reed, ed.; Wiley VCH:Weinheim, 2010, specifically see p. 9.

2 For recent reviews on stereogenic quaternary carbon formation, see: (*a*) O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873–888; (*b*) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369–396; (*c*) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473–1482.

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4 One 5 mol% catalyst loading example was demonstrated, see ref. 3c: isobutyraldehyde/β-nitrostyrene (2 : 1), 5 mol% catalyst loading, 22 h, 99% yield, 76% *ee*.

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8 10 mol% catalyst loading. For lead references of those methods requiring ≤5 equiv of an α,α-substituted aldehyde and providing ≥84% *ee*, see ref. 3e, 7, and: (*a*) J. Xiao, F.-X. Xu, Y.-P. Lu and T.-P. Loh, *Org. Lett.*, 2010, **12**, 1220–1223; (*b*) P. Li, L. Wang, M. Wang and Y. Zhang, *Eur. J. Org. Chem.*, 2008, 1157–1160; (*c*) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 4966–4967.

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10 20 mol% catalyst loading. For lead references of those methods requiring ≤ 4 equiv of an α,α-substituted aldehyde and providing ≥85% *ee*, see ref. 6 and: (*a*) M. Yoshida, A. Sato and S. Hara, *Org. Biomol. Chem.*, 2010, **8**, 3031–3036; (*b*) C. Chang, S.-H. Li, R. J. Reddy and K. Chen, *Adv. Synth. Catal.*, 2009, **351**, 1273–1278; (*c*) X.-j. Zhang, S.-p. Liu, J.-h. Lao, G.-j. Du, M. Yan and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2009, **20**, 1451–1458; (*d*) X.-j. Zhang, S.-p. Liu, X.-m. Li, M. Yan and A. S. C. Chan, *Chem. Commun.*, 2009, 833–835; (*e*) Q. Zhang, B. Ni and A. D. Headley, *Tetrahedron*, 2008, **64**, 5091–5097; (*f*) A. Sato, M. Yoshida and S. Hara, *Chem. Commun.*, 2008, 6242–6244.

11 Ref. 6,10a,c,d,f report ≥98% *ee* for the reaction of isobutyraldehyde (2.0 to 3.7 equiv, 20 mol% cat. loading) with β-nitrostyrene.

12 For a 30 mol% example, see ref. 5.

13 To our knowledge the use of < 2.0 equiv of an α,α-branched aldehyde has only been elaborated on by Yoshida, see Table 4 (only entry 2) of ref. 10a.

14 (*a*) L.-q. Gua and G. Zhaoa, *Adv. Synth. Catal.*, 2007, **349**, 1629–1632; (*b*) B. M. Choudary, Ch. V. Rajasekhar, G. G. Krishna and K. R. Reddy, *Synth. Commun.*, 2007, **37**, 91–98.

15 A single α,α-substituted aldehyde was studied, isobutyraldehyde/β-nitrostyrene (3 : 1), 5 mol% catalyst loading, 84 h, 71% yield, 85% *ee*, see Supp Info (page S-6†) of: T. Mandal and C.-G. Zhao, *Angew. Chem., Int. Ed.*, 2008, **47**, 7714–7717.

16 For example, see: (*a*) M. Hernández-Rodríguez and E. Juaristi, *Tetrahedron*, 2007, **63**, 7673–7678; (*b*) G. M. Kyne, M. E. Light, M. B. Hursthouse, J. de Mendoza and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1258–1263; (*c*) B. C. Hamann, N. R. Branda and J. Rebek, Jr., *Tetrahedron Lett.*, 1993, **34**, 6837–6840.

17 The preformed lithium salt of isoleucine/urea (5 : 5 or 10 : 10 mol%) resulted overwhelmingly in by-product formation.

18 Squaramide is an interesting new hydrogen bond donor, the parent primary diamine would be interesting to examine, see: J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416–14417.

19 Interesting to examine will be: amino acids related to isoleucine and L-threonine, alternative O-protected threonines, and β-amino acids. It can be further imagined that replacing the carboxylic acid moiety of amino acids with a sulfate or phosphate ester, or a phosphonate or sulfonate moiety will be valuable to pursue.

20 M. Kotke and P. R. Schreiner, (Thio)urea Organocatalysts. In *Hydrogen Bonding in Organic Synthesis*, P. M. Pihko, Ed.; Wiley-VCH: Weinhein, 2009, p. 141–352.

21 J. Wang, H. Li, B. Lou, L. Zu, H. Guo and W. Wang, *Chem.–Eur. J.*, 2006, **12**, 4321–4332.

22 See ref. 5: cyclohexylcarboxaldehyde/β-nitrostyrene (2 : 1), 30 mol% loading, 96 h, 90% yield, 59% *ee*.

23 See ref. 21: cyclohexylcarboxaldehyde/β-nitrostyrene (10 : 1), 20 mol% loading, 96 h, 42% yield, 64% *ee*.

24 (*a*) D.-Q. Xu, H.-D. Yue, S.-P. Luo, A.-B. Xia, S. Zhang and Z.-Y. Xu, *Org. Biomol. Chem.*, 2008, **6**, 2054–2057; (*b*) Z.-B. Li, S.-P. Luo, Y. Guo, A.-B. Xia and D.-Q. Xu, *Org. Biomol. Chem.*, 2010, **8**, 2505–2508.

25 To see all of Demir's relevant research, see: (*a*) A. S. Demir and S. Eymur, *Tetrahedron: Asymmetry*, 2010, **21**, 405–409; (*b*) A. S. Demir and S. Eymur, *Tetrahedron: Asymmetry*, 2010, **21**, 112–115; (*c*) Ö. Reis, S. Eymur, B. Reis and A. S. Demir, *Chem. Commun.*, 2009, 1088–1090.

26 Demir's quaternary carbon bond formation conditions and results: isobutyraldehyde/β-nitrostyrene (3 : 1), 20 mol% proline/20 mol% Schreiner's thiourea, 36 h, 66% yield, 72% *ee*, as found in ref. 25b.

27 Related self-assembly based approaches characterize other reactions, for an aldol reaction and an α-hydroxylation of aldehydes, see respectively: (*a*) X. Company, G. Valero, L. Crovetto, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 6564–6568; (*b*) S. L. Poe, A. R. Bogdan, B. P. Mason, J. L. Steinbacher, S. M. Opalka and D. T. McQuade, *J. Org. Chem.*, 2009, **74**, 1574–1580.

28 (*a*) Sulfonamides and sulfamides are already established as strong hydrogen bond donors, see: A. A. Rodriguez, H. Yoo, J. W. Ziller and K. J. Shea, *Tetrahedron Lett.*, 2009, **50**, 6830–6833; (*b*) O. Mammoliti, S. Allasia, S. Dixon and J. D. Kilburn, *Tetrahedron*, 2009, **65**, 2184–2195.

29 See for example: (*a*) C. G. Kokotosa and G. Kokotos, *Adv. Synth. Catal.*, 2009, **351**, 1355–1362; (*b*) D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, *Adv. Synth. Catal.*, 2006, **348**, 826–832.

30 Depictions of nitro groups hydrogen bonding to thioureas are normally drawn with both N–H groups of the thiourea and both oxygen atoms of the nitro group coplanar and hydrogen bonded, for example see: ref. 20 and ref. 31 Some debate remains in the literature, with a 2006 computational study suggesting a 'one oxygen model' (see ref. 29b) and other groups having variously used this model (see ref. 6). Our depicted and favored transition state model, synclinical I (Fig. 2), can only accommodate a one oxygen activation model.

31 S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418–5427.

32 Orbital activation of the nitroalkene alone, *e.g.* a nitroalkene, sulfamide pair independent of the carboxylate moiety is unlikely. This is borne out by performing the reaction in the absence of a base; the nitroalkene, sulfamide pair would still exist, yet no product formation was noted (Table 1, entry 11).

33 (*a*) A. Risaliti, M. Forchiassin and E. Valentin, *Tetrahedron*, 1968, **24**, 1889–1898; (*b*) F. P. Colonna, E. Valentin, G. Pittaco and A. Risaliti, *Tetrahedron*, 1973, **29**, 3011–3017; (*c*) E. Valentin, G. Pittaco, F. P. Colonna and A. Risaliti, *Tetrahedron*, 1974, **30**, 2741–2746; (*d*) S. Fabrissin, S. Fatutta and A. Risaliti, *J. Chem. Soc., Perkin Trans. 1*, 1981, 109–112.

34 D. Seebach and J. Goliński, *Helv. Chim. Acta*, 1981, **64**, 1413–1423.