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Noncovalent Bifunctional Organocatalysts: Powerful Tools for Contiguous Quaternary-Tertiary Stereogenic Carbon Formation, Scope, and Origin of Enantioselectivity

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Abstract: Relying on the assembly of commercially available catalyst building blocks, highly stereocontrolled quaternary carbon (all carbon substituted) formation has been achieved with unmatched substrate diversity. For example, the in situ assembly of a tricomponent catalyst system allows α-branched aldehyde addition to nitroalkene or maleimide electrophiles (Michael products), while addition to an α-iminoester affords Mannich reaction products. Very good yields are observed and for fifteen of the eighteen examples 96–99% *ee* is observed. Using racemic α-branched aldehydes, two contiguous (quaternary–tertiary) stereogenic centers can be formed in high diastereo- and enantiomeric excess (eight examples) via an efficient in situ dynamic kinetic resolution, solving a known shortcoming for maleimide electrophiles in particular. The method is of practical value, requiring only 1.2 equiv of the aldehyde, a 5.0 mol% loading of each catalyst component, for example, O-*t*Bu-L-threonine (O-*t*Bu-L-Thr), sulfamide, DMAP or O-*t*Bu-L-Thr, KOH, and room temperature reactions. As a highlight, the first demonstration of ethylisovaleraldehyde (**7**) addition is disclosed, providing the most congested quaternary stereogenic carbon containing succinimide product (**8**) known to date. Finally, mechanistic insight, via DFT calculations, support a noncovalent assembly of the catalyst components into a bifunctional catalyst, correctly predict two levels of product stereoselectivity, and suggest the origin of the tricomponent catalyst system's exceptionality: an alternative hydrogen bond motif for the donor-acceptor pair than currently suggested for non-assembled catalysts.

Keywords: computational chemistry · maleimide · Mannich reaction · organocatalysis · quaternary carbon

Introduction

The high selectivities of enzymes are generally attributed to their folded and coiled protein architectures which impose pin point noncovalent attractive and repulsive forces, while also exploiting temporary (activating) covalent bonds, to control the size, trajectory, facial approach, and conformation of reacting chemical partners. In recent years, chemists have been mimicking these control mechanisms, albeit with simple organic molecules lacking the atom inefficient scaffolds of nature's catalysts. Using organocatalysts they have shown: expanded substrate scope, greater reaction diversity, and at times chemical selectivities on par with enzymes.[1]

The field of organocatalysis was reinvigorated, in large part, by the examination of simple single amino acids over ten years ago.[2] Since then, a decade of tailor designed catalysts has ensued, producing more complex organocatalysts that strongly outperform amino acids regarding starting material stoichiometry, catalyst loading, reaction time, yield, and stereocontrol.[3] Yet single amino acids remain appealing,[4–6] especially so because they are commercially available, diverse, and require no synthesis.

Here we show that single amino acids have regained their status as the best performing catalysts, with rare exception, for the outlined Michael and Mannich reactions. To accomplish this we have augmented the natural attributes of amino acids by selectively binding their carboxylate moiety, in situ, to a hydrogen-bond donor (Scheme 1). The resulting bifunctional catalyst has a catalytically active primary amine and hydrogen bond donor site for the respective activation of a carbonyl and an electrophile. This approach represents a rare example of a highly efficient catalyst relying on the self-assembly of purely organic components to permit the higher ordered task of a conventional (covalently formed) bifunctional organocatalyst. Finally, the simplicity and known availability of the catalyst building blocks used here raises the question of whether these or similar systems were among precursor catalysts to enzymes, enabling increased molecular diversity on a prebiotic earth.[7]

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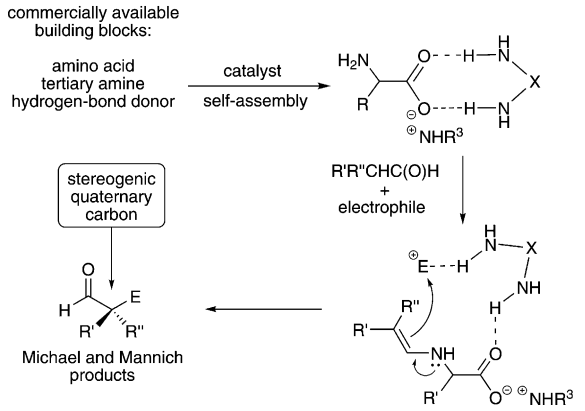


Scheme 1. Assembly based bifunctional catalyst concept.

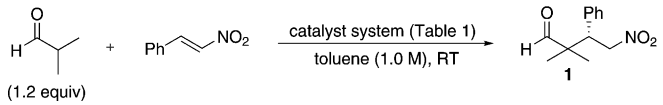
Results and Discussion

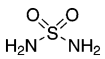
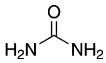
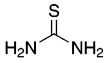
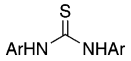
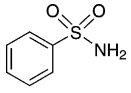
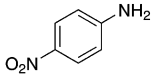
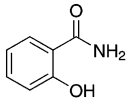
Quaternary carbon bond formation remains formidable.[8] It is consequently unsurprising that a limited number of α-branched carbonyl additions, versus unbranched carbonyl additions, have been reported. The challenge, as seen from a broader context, is the lack of organocatalytic examples with practical reaction conditions regarding natural product or pharmaceutical drug applications. To address this, an across-the-board multi-parameter improvement in starting material stoichiometries, catalyst loading (turn-over number and frequency implicit), and reaction time, with excellent reaction product profiles, is required. Here we have come one step closer to this idealized goal.

In a recent communication we reported the addition of α-branched aldehydes to aryl or alkyl substituted-β-nitroalkenes.[9,10] Here we show the ease of fine tuning the catalyst system for new reaction types, and use DFT calculations to elicit the first understanding for the synergy arising when combining an amino acid, a hydrogen-bond donor, and a base for catalysis.

Table 1 details an expanded catalyst study of the model Michael reaction, isobutyraldehyde addition to *trans*-β-nitrostyrene. We previously identified DMAP as superior to imidazole, DABCO, DBU, *N*-methylmorpholine, iPr_2NEt, and Et_3N. Holding the amino acid (O-*t*Bu-L-threonine) and hydrogen-bond donor (sulfamide) constant, DMAP was also found to be superior to common alkali hydroxides (Table 1, entries 1–3 and Supporting Information). Furthermore, for these tricomponent catalyst systems, the superior qualities of the sulfamide hydrogen-bond donor have been reaffirmed. For example, the known hydrogen-bond donors urea, thiourea, and Schreiner's thiourea (Ar = -3,5-$(CF_3)_2$-phenyl), can approach the usefulness of sulfamide, but provide lower yield and/or *ee* (compare entry 1 to 4–6); while previously uninvestigated hydrogen bond donors (entries 7–13) have proven to be less effective but show potential for future exploitation, for example, salicylic amide enables an extremely fast reaction (entry 13). For an extensive list of all examined hydrogen-bond donors, see the Supporting Information. Examination of the corresponding bicomponent catalyst systems, that is, without the presence of a hydrogen-bond donor, resulted in reduced yields and *ee* values (Table 1, entries 14–17). Finally, when the catalyst system is reduced to O-*t*Bu-L-Thr alone (entry 18), only starting material is observed after the extended reaction time of 18 h. In brief, the catalyst system of O-*t*Bu-L-Thr, sulfamide, DMAP remains the best currently known for the addition of a broad range of α-branched aldehydes to aryl or alkyl substituted-β-nitroalkenes based on all measurable parameters,

Table 1. Nitroalkene additions: expanded catalyst system investigations.



Entry	Catalyst system: O-*t*Bu-L-Thr (5 mol%) + additive(s) base (5 mol%)	HBD[c] (5 mol%)	*t* [h]	Yield [%][a]	*ee* [%][b]
1	DMAP		7	98	98
2	LiOH		5	>99	96
3	KOH		4	>99	94
4	DMAP		7	23	88[11]
5	DMAP		7	60	88[11]
6	DMAP		3	100	94
7	DMAP		7	4	80
8	KOH		7	98	80
9	DMAP		7	48	81
10	KOH		7	93	79
11	DMAP		7	24	90
12	KOH		6	100	87
13	KOH[d]		2	98	65
14	DMAP	–	7	8	86
15	LiOH	–	7	60	92
16	LiOH[d]	–	7	76	91
17	KOH	–	7	67	91
18	–	–	18	<1	–

[a] HPLC area% yields. [b] Determined by chiral HPLC analysis (OD-H chiral column). [c] hydrogen bond donor (HBD). [d] 10 mol% used.

for example, catalyst loading, starting material stoichiometry, and product profile.[9]

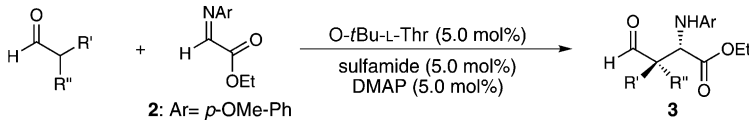
Despite the vast number of organocatalyzed Mannich reactions reported to date,[12] scant attention has been given to those producing a quaternary carbon in the β-amino aldehyde product.[13] Table 2 provides a summary of our Mannich reaction products **3a**–**d** between α-iminoethyl glyoxalate (**2**) and two symmetrical (achiral) and two unsymmetrical (racemic) α-branched aldehydes. Using the tricomponent catalyst system (O-*t*Bu-L-Thr, sulfamide, DMAP) a synthetically useful aldehyde stoichiometry (1.2 equiv) could be realized with the lowest reported catalyst loading (5.0 mol%) and short reaction times (6 or 12 h). Entries 1, 2, and 4 (Table 2) delineate the best current product profiles, albeit **3d** is a new compound and reported here for the first time. Barbas and co-workers, who pioneered this and many other organocatalyzed reactions, reported a more favorable product profile for **3c**[14] compared to our data (Table 2, entry 3). Unlike the other reactions detailed in this manuscript, all Mannich reactions required the addition of 5 Å molecular sieves.[15]

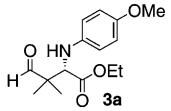
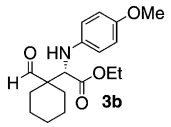
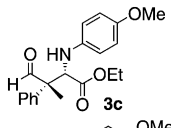
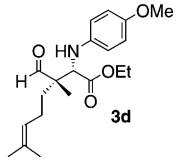
It is instructive to note that replacing sulfamide with thiourea, that is, using O-*t*Bu-L-Thr, thiourea, DMAP, resulted in gross by-product formation, ~40 area% (HPLC), and lower product *ee* (92%) for **3a**. Similar low yields resulted when holding O-*t*Bu-L-Thr and sulfamide constant, but exchanging DMAP with LiOH or KOH, respectively, providing 80% and 85% *ee* for Mannich product **3a**. Finally, examination of catalyst systems lacking a hydrogen-bond donor essentially shutdown the reaction, for example, the bicomponent catalyst systems of O-*t*Bu-L-Thr, DMAP or O-*t*Bu-L-Thr, KOH provided <5 area% and <15 area% (HPLC), respectively, of product **3a** after 6 h (the optimal reaction time). In conclusion, for Mannich product formation, the only synthetically viable catalyst system is: O-*t*Bu-L-Thr, sulfamide, DMAP.

The addition of in situ generated enamines to maleimide electrophiles allows access to chiral pyrrolidinediones (succinimides). These products, and the reduction products thereof, chiral pyrrolidines and pyrrolidinones (δ-lactams),[16] are core structural units found within natural products and some clinical drug candidates.[17,18] When the nucleophilic carbonyl (enamine) is an α-branched aldehyde, increased molecular complexity is featured in the succinimide product, that is, an all carbon substituted quaternary carbon is present. Cordova and co-workers were the first to demonstrate this possibility when he added isobutyraldehyde to *N*-phenylmaleimide, but the yield and *ee* were low.[19] In 2010 three more reports appeared, each employing a monothiourea of *trans*-1,2-diaminocyclohexane as the organocatalyst.[20] In general, these reports expanded the substrate scope while providing very good to excellent yields and *ee* values, but the aldehyde stoichiometries (2–10 equiv) and catalyst loadings (5–20 mol%) can be improved. Additionally, when forming contiguous quaternary–tertiary stereogenic centers, a glaring lack of diastereocontrol was noted for the current methods and higher catalyst loadings were required.[21] Here we show that this problem has been largely solved and do so with the greater substrate diversity.

Building on our catalyst knowledge from the examination of nitroalkenes (Table 1) and Mannich precursors (Table 2), we were surprised to find not one, but several reaction conditions allowing excellent product profiles, for **6a**, when adding isobutyraldehyde to *N*-phenylmaleimide (Table 3, entries 1–4).[22] For example, the tricomponent catalyst system of O-*t*Bu-L-Thr (5 mol%), thiourea (5 mol%), DMAP (5 mol%) proved to be very useful (Table 3, entry 3), while the same catalyst system was deemed to be of lower value when examining nitroalkenes, and of no practical value when examining the α-iminoethyl glyoxalate electrophile (Mannich reaction). In the end, succinimide product formation was found to be optimal when using one of the following two catalyst systems: i) O-*t*Bu-L-Thr

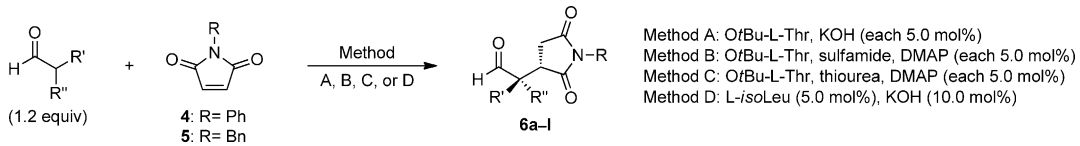
Table 2. Quaternary carbon containing Mannich products of α-iminoethyl glyoxalate.[a]

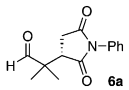
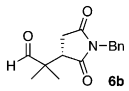
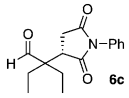
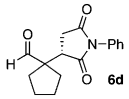
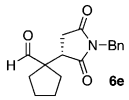
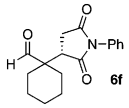
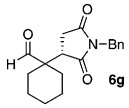
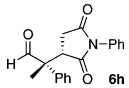
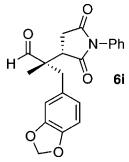
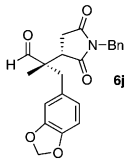
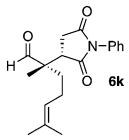
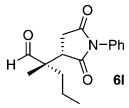


Entry	Product	Aldehyde (equiv)	T [°C]	t [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	 **3a**	1.2	23	6	92	–	97
2	 **3b**	1.2	23	6	72	–	96
3	 **3c**	1.5	0	12	84	3:1	79/84[e]
4	 **3d**	1.2	0	12	90	4:1	99/99[e]

[a] Aldehyde (0.6 mmol), imine (0.5 mmol), CH_2Cl_2 (1.0 M), O-*t*Bu-L-Thr (5 mol%), DMAP (5 mol%), sulfamide (5 mol%), 5 Å M.S. (50 mg). [b] Isolated yield. [c] Determined by chiral HPLC analysis (AS-H column) of the crude product. [d] Determined by chiral HPLC analysis (AS-H column) after silica gel purification. [e] *ee* of major diastereomer/*ee* of minor diastereomer.

Table 3. Quaternary carbon containing succinimide products.[a]



Entry	Method	Product	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	A	 **6a**	4	96	–	>99
2	B		6	91		96
3	C		5	81		94
4	D		14	93		98
5	B	 **6b**	5	94	–	97
6	A	 **6c**	6	96	–	>99
7	B	 **6d**	16	93	–	97
8	B	 **6e**	11	86	–	99
9	B	 **6f**	20	77	–	97
10	B	 **6g**	20	80	–	96
11	A	 **6h**	10	86	>99:1	94
12	B		24	82	>99:1	92
13	C		24	81	>99:1	92
14	A	 **6i**	4	89	96:4	>99
15	B		20	84	93:7	98
16	A	 **6j**	4	87	97:3	98
17	B		16	89	97:3	94
18	A	 **6k**	4	94	92:8	>99/>99[e]
19	B		5	98	90:10	>99/>99[e]
20	B	 **6l**	16	88	74:26	98/86[e]

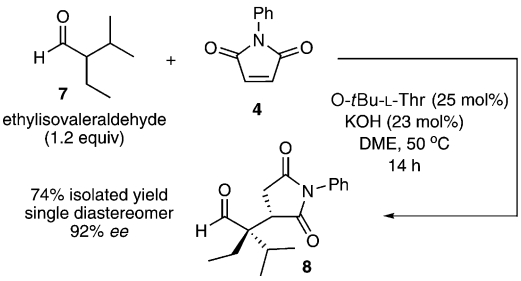
[a] Reaction conditions: maleimide (1.0 mmol, 1.0 equiv), aldehyde (1.2 equiv), CH_2Cl_2 (2.0 M), 23 °C. [b] Isolated yield data after column chromatography. [c] Determined by chiral HPLC analysis on the crude reaction product.[25] [d] Determined by chiral HPLC analysis after silica gel purification. [e] *ee* of major diastereomer/*ee* of minor diastereomer.

(5 mol%), KOH (5 mol%) or ii) O-*t*Bu-L-Thr (5 mol%), sulfamide (5 mol%), DMAP (5 mol%), Table 3 (entries 1 and 2).[23] It is also noteworthy that L-isoleucine can replace O-*t*Bu-L-Thr and provided an excellent product profile, albeit with a longer reaction time (Table 3, compare entry 4 with 1 and 2). Further note that the use of O-*t*Bu-L-Thr (5 mol%) alone resulted in recovered starting materials after 18 h.

Many substrates are outlined in Table 3 and represent a broad set of α-branched aldehyde additions to *N*-phenyl- and *N*-benzylmaleimides. Compounds **6e**, **6g**, **6i**, and **6j** are reported here for the first time. Taken in total, the product profiles can be characterized as excelling, in particular, because of very good yields, short reaction times, and high stereoselectivity, while only requiring 5 mol% of the catalyst system and 1.2 equiv of the aldehyde. In particular entries 11–20 are of far reaching consequence because they demonstrate the first examples of excellent diastereocontrol, a known shortcoming of this reaction which is now discussed.[21]

For the formation of two contiguous (quaternary–tertiary) stereogenic centers, the addition of racemic α-substituted aldehydes is required, and high product d.r., and *ee*, is made possible via an efficient in situ dynamic kinetic resolution. For example hydratropaldehyde addition provided succinimide **6h** (Table 3, entry 11) as one diastereomer in 86% yield with 94% *ee* within 10 h (5 mol% catalyst loading), no other catalyst system can achieve similar results.[24] Using a less hindered α-branched aldehyde, substituent is an α-benzyl derivative, an 89% yield of **6i** was achieved with a 96:4 d.r. and >99% *ee* in 4 h (Table 3, entry 14). Examination of the same aldehyde with N-benzylmaleimide, instead of *N*-phenylmaleimide, resulted in **6j** with a 97:3 d.r. (entry 16). Further reduction of the steric bulk of the larger α-subsubstituent on the aldehyde starting material, for example, as in product **6k** (entry 18), led to very good d.r. (92:8), with high yield (94%) and *ee* (>99%) within 4 h, exceeding the reported d.r. of 2:1.[20b] Finally, examination of 2-methylpentanal revealed a mediocre d.r. (74:26), nonetheless this ratio would be considered high when it is noted that a methyl group has been differentiated from an *n*-propyl moiety, and this represents an improvement over the best reported d.r. of 1:1.[20b]

The above results demonstrate that quaternary carbons, all carbon substituted, can be formed with relative ease, and compounds **6c** (entry 6) and **6h** (entry 11) reveal that congested quaternary carbons can be formed in high yield. Nevertheless, to better appreciate the steric limitations of the current method, we investigated the addition of ethylisovaleraldehyde (**7**), a highly congested aldehyde (Scheme 2). Under our standard reaction conditions no product was observed, but solvent and temperature screening (see Supporting Information) showed 1,2-dimethoxyethane to be optimal at 50°C over 14 h, forming product **8** which was isolated in diastereopure form in 74% yield (92% *ee*). Product 8 is significant because it represents the most sterically crowded succinimide formed to date. In summary, these combined examples represent the most diverse set of α-branched aldehyde additions known.

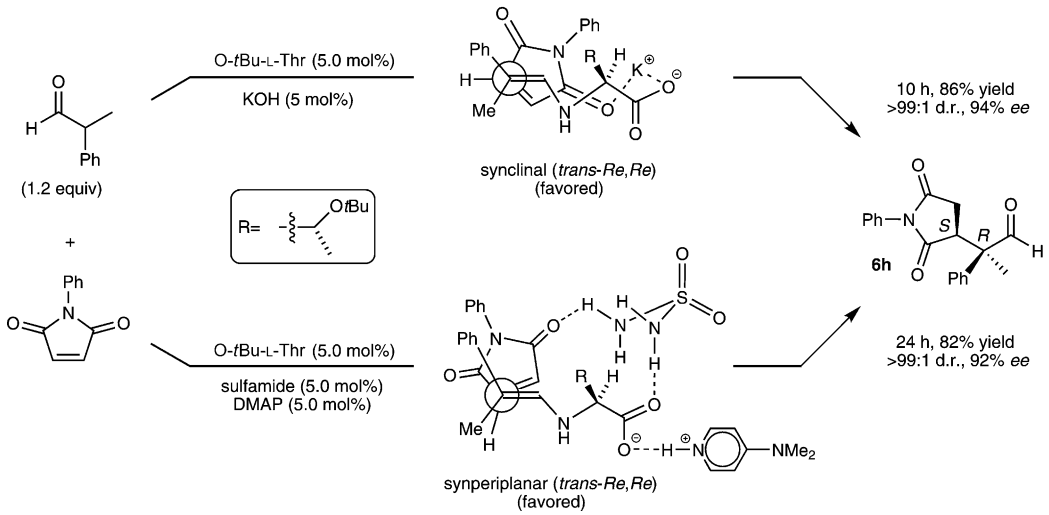


Scheme 2. Congested quaternary carbon formation: first demonstration of 2-ethyl-3-methylbutanal (**7**) addition.

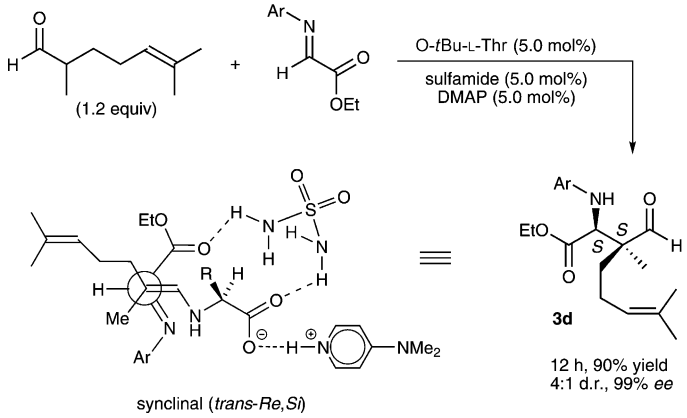
In our opening communication on nitroalkenes,[9] we speculated that a synclinal approach of the electrophile and enamine best accounted for the observed diastereo- and enantiocontrol. Here we have used DFT studies to obtain greater insight into the complexes leading to product formation, and the unique role hydrogen bonding is playing in the tricomponent catalyst system (O-*t*Bu-L-Thr, sulfamide, DMAP) versus potassium activation in the bicomponent catalyst system (O-*t*Bu-L-Thr, KOH). Those findings, discussed shortly, support a synperiplaner approach of maleimide via two critical, bridging, hydrogen bonds: $oxygen_{maleimide}\cdots H\text{-}N_{sulfamide}$ and $N\text{-}H_{sulfamide}\cdots oxygen_{carboxylate}$ (Scheme 3, bottom). For the bicomponent system, O-*t*Bu-L-Thr, KOH, a synclinal approach was found to be optimal (Scheme 3, top). Regarding the iminoester electrophile (Mannich reaction) it can be speculated that a synclinal approach is favored (Scheme 4).

Importantly, these models (Schemes 3 and 4) support our conclusions regarding the diastereo- and enantiocontrol for both the maleimide and iminoester electrophiles, and the stereochemistry has been corroborated by comparison with earlier reported chiral HPLC data (see Supporting Information). In the case of structure **6k** (Table 3, entries 18 and 19), unambiguous relative and absolute stereochemistry was established via X-ray crystallographic analysis (Figure 1). Based on this larger body of stereochemical findings, we have similarly assigned the stereochemistry for the six newly identified compounds, **3d**, **6e**, **6g**, **6i**, **6j**, and **8**. Within the context of this mechanistic discussion, it is noteworthy that Barbas et al.[6b,e] and Yoshida et al.,[5] among others, have meaningfully contributed to the conceptual development of amino acid catalyzed reaction models, albeit for systems without the intermediacy of a hydrogen-bond donor as noted here (Schemes 3 and 4).

To better appreciate the reaction pathways leading to the above noted products, we simulated the reaction of hydratropaldehyde with *N*-phenylmaleimide (Scheme 3). The succinimide product thereof, **6h**, was chosen for two major reasons: i) the product can be formed using three different catalyst systems (Table 3, entries 11–13), consequently insight into the nuances of each complex can be evaluated; and ii) the model would have to predict two levels of stereoselectiv-



Scheme 3. DFT supported intermediates: correctly predict stereochemical outcome for hydratropaldehyde addition to maleimide.



Scheme 4. Postulated reaction intermediate: correctly predicts 2,6-dimethylhept-5-enal addition to an α-iminoester.

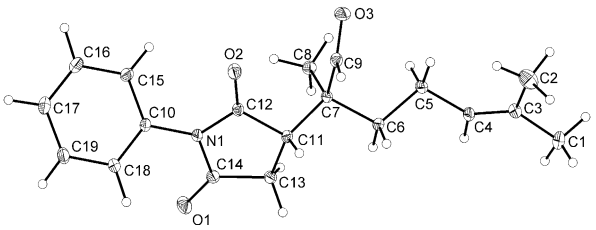


Figure 1. ORTEP diagram of (*S*,*S*)-**6k**, Table 3, (50% probability ellipsoids): O-*t*Bu-L-Thr, sulfamide, DMAP catalyst system.

ity, that is, the diastereo- and enantiocontrol imposed during the carbon–carbon bond forming step.

The reaction can be thought of as working in two steps: first, van der Waals complexes (complexes), where reactants and catalyst are held together by temporary covalent bonds (aldehyde activation to an enamine) and hydrogen bridges (maleimide-to-hydrogen-bond donor and hydrogen bond donor-to-carboxylate), are formed in the liquid phase. These complexes are local minima, relatively stable, and are the key to understanding the chemical reactions that take place. Consequently, they represent species in which the reacting centers are in close proximity for appreciable amounts of time and will govern the preferred stereochemical pathways. The second step of the reaction is a straightforward bond formation process, a chemical reaction transforming the complex into the product.

Our computational study concentrates on step one, to understand the structure and stability of the complexes of reactants and catalyst, while step two, responsible for the reaction rates, is the subject of a future study. The simulation of multi-component assemblies is not trivial, and this work represents the first attempt to model these intricate systems. As the quantitative description of hydrogen bonds is crucial for this study, we employed density functional theory with empirical corrections for London dispersion (BP86-D)[26] together with the all electron TZP basis as implemented in the ADF code.[27] Free enthalpies have been calculated using the harmonic approximation and solvent effects have been accounted for using COSMO.[28]

Assembly of the tricomponent catalyst system, O-*t*Bu-L-Thr, sulfamide, DMAP, is assumed to be facial. Experimentally this is convincing because the catalyst components readily dissolve but only when all three are present in equamolar quantities in the presence of the starting materials. The tricomponent assembly itself, is calculated to be robust by DFT (Supporting Information, Computational Sections 1 and 2). Accordingly, our study began by modeling *trans* enamine attack on maleimide with a Re_{enamine}, $Re_{\text{maleimide}}$ facial approach (Scheme 3); and conversely with a Si_{enamine}, $Re_{\text{maleimide}}$ facial attack for the *cis* enamine. This is a reasonable starting point because, if supported by DFT calculations, it would: i) explain the diastereo- and enantioselectivity for the major and minor products; ii) differentiate synclinal from synperiplanar approaches; iii) account for the fate of both the *cis* and *trans* enamines; and iv) support, or refute,

the propensity of the maleimide electrophile to preorganize (hydrogen bond) at the assembled catalyst's hydrogen bond donor site (sulfamide).

Four low energy *trans* enamine complexes (**A**, **B**, **C**, **D**) were identified, with relative energy differences (ΔG) of 0, 0.56, 1.03, and 1.50 kcal mol^{-1}. All four complexes (Figure 2)

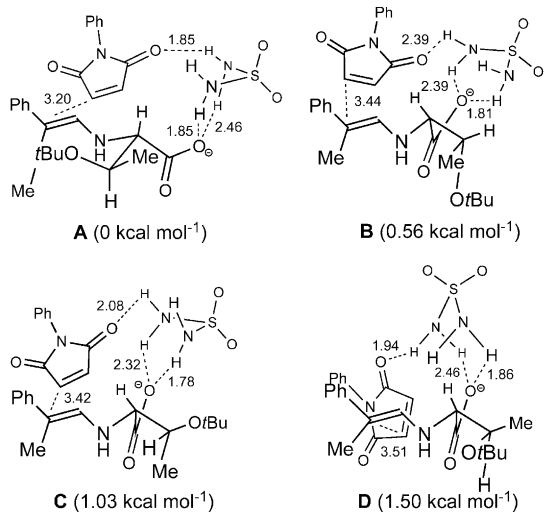


Figure 2. Hydratropaldehyde addition to maleimide, complexes for **6h** (Table 3, entry 12): O-*t*Bu-L-Thr, sulfamide, DMAP catalyst system.

reveal a $Re_{enamine}$, $Re_{maleimide}$ facial attack and are enabled by two critical, bridging, hydrogen bonds.[29] For visualization purposes, the protonated DMAP counter ion is excluded from the drawn complexes in Figure 2, but all conclusions were reached after thorough examination of the three dimensional representations containing DMAP. Computational snapshots including DMAP can be found in the Supporting Information (Computational Section 3, Figure S3). Furthermore, all unmarked hydrogen bonds (Figures 2 and 4) were found to be >2.90 Å.

The lowest energy complex (**A**) displays a linear arrangement of threonine's carboxylate, α-carbon, and nitrogen, with the enamine (aldehyde) atoms (Figure 2, **A**). This conformation, which is stabilized by a 2.15 Å intramolecular hydrogen bond (not marked), N-H$_{enamine}$···OC(O)R$_{carboxylate}$, jettisons the β-carbon of threonine to the *Si* face of the enamine where the O*t*Bu group blocks this face.

Because the assembled sulfamide engages in hydrogen bonding with only one of the carboxylate oxygens,[30] it has the rotational freedom to place its remaining NH_2 hydrogen bonding unit in a plane parallel to the unoccupied *Re* face of the enamine (Figure 2, **A**). Here, maleimide participates in hydrogen bond donor–acceptor pairing with the sulfamide NH_2 group via a convincingly robust hydrogen bond (1.85 Å). This pairing has the consequence of placing the electrophilic carbon of maleimide within bonding distance proximity (3.20 Å) of the nucleophilic enamine carbon (Figure 2, complex A).

The three remaining, higher energy, complexes (**B**, **C**, **D**) share a common conformational feature, the enamine and threonine's α- and β-carbons are in the same plane, but now the carboxylate moiety is approximately perpendicular to the *Re* face of the enamine. In response, the assembled sulfamide component rotates by an equal degree, again aligning maleimide in a plane parallel to the *Re* face of the enamine, albeit at an increased carbon-carbon pre-bond forming distance (3.42–3.51 Å) for complexes **B**, **C**, **D** as compared to complex **A** (3.20 Å). In two of the complexes, **B** and **C**, the O*t*Bu group is essentially contiguous with the plane containing the enamine, that is, no moiety blocks the *Si* face of the enamine; while in complexes **A** and **D** the O*t*Bu group blocks the *Si* face. As found for complex **A**, complexes **B**–**D** have a $Re_{enamine}$, $Re_{maleimide}$ facial approach, thus all four complexes (**A**–**D**) lead to the same major product (*S*,*R*)-**6h** (Scheme 3). Finally, four *cis* enamine complexes (analogous to complexes **A**–**D**, Figure 2) were additionally identified for the O-*t*Bu-L-Thr, sulfamide, DMAP catalyst system. Of those, the lowest energy *cis* complex was 4.34 kcal mol^{-1} greater in energy than *trans* enamine **A** (Figure 2), making analysis of the *cis* enamines inconsequential, see Supporting Information (Computational Section 3, Table S7).

It is noteworthy that these energy optimized complexes always choose to participate in hydrogen bonding, and when doing so, the catalyst's sulfamide component becomes the preeminent handle regarding stereocontrol. In complexes **A**–**D** the carboxylate–sulfamide unit is always directed to the *Re* face of the enamine, and there it directs the *Re* face of maleimide within bonding distance proximity of the enamine ($Re_{enamine}$, $Re_{maleimide}$ approach). A *Si* face approach of maleimide, that is, $Re_{enamine}$, $Si_{maleimide}$, is unattainable under the organization of hydrogen bonding due to the overwhelming steric impediment imposed by the *N*-phenyl moiety of *N*-phenylmaleimide. These findings provide a conceptual basis for understanding the very high stereoselectivity (>99:1 d.r., 96:4 e.r.) noted for this reaction.

An open question is the viability of a purely steric based reaction pathway, that is, the random approach of maleimide, without the aid of hydrogen bonding, onto the enamine. Entropically this reaction pathway is less competitive with product formation via preorganization with hydrogen bonding. Regardless, it is important to model this possibility. For this analysis, complexes **A**–**D** (Figure 2) are of little value, even though, for example, complexes **B** and **C** have an accessible *Si* enamine face, because they represent intermediates that already contain a highly integrated maleimide molecule. A more realistic approach is to consider the same complexes, albeit modeled without the presence of maleimide, and then consider the facial approach of maleimide on the enamine without the aid of hydrogen bonding. In the event, four energy optimized *trans* enamine complexes (hydratropaldehyde, O-*t*Bu-L-Thr, sulfamide, DMAP) were observed. Of those, the lowest energy complex (**E**), Figure 3, has a relative energy difference (ΔG) with the next lowest complex of 11.3 kcal mol^{-1}, see Supporting Information

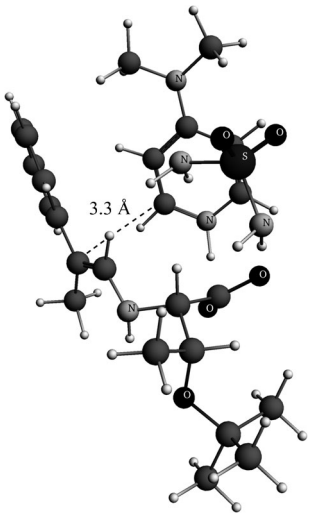


Figure 3. Steric based model, low energy complex **E**: hydratropaldehyde, O-*t*Bu-L-Thr, sulfamide, DMAP.

(Computation Section 7, Table S32). This extremely large energy difference focuses the analysis to complex **E** alone (Figure 3);[31] its *Re* enamine face is completely blocked by the protonated DMAP counter ion, while the *Si* face (enamine) is exposed. This leaves the *Si* enamine face open to attack by maleimide, but the two possible approaches, $Si_{enamine}$, $Re_{maleimide}$ and $Si_{enamine}$, $Si_{maleimide}$, do not lead to the major product, (*S*,*R*)-**6h**, which is formed in good yield (82%) and with high stereoselectivity (>99:1 d.r., 92% *ee*).

Finally, it is possible that a steric based reaction pathway could occur via a complex without sulfamide, that is, maleimide attack on a complex of only hydratropaldehyde, O-*t*Bu-L-Thr, DMAP (no bound sulfamide). This is less probable for two reasons: i) sulfamide is expected to have a high binding constant for the carboxylate,[32] suggesting that sulfamide will more often be bound, for example, as in complex **E** (Figure 3), than not, and ii) experimentally, there is little support for this hypothesis. Regarding the last point, performing the reaction, which normally takes 24 h (Table 3, entry 12), *without* sulfamide provided **6h** in 29 area% yield (HPLC), 4:1 d.r., and 92% *ee*, over 24 h.[33]

The above findings can be summarized as follows. A $Re_{enamine}$, $Re_{maleimide}$ reaction pathway, via a hydrogen bond donor–acceptor pair (maleimide···sulfamide, Figure 2), overcomes the entropic disadvantage of maleimide's random approach (steric model) onto the enamine, selectively forming (*S*,*R*)-**6h** (Scheme 3). The high propensity for the $Re_{enamine}$, $Re_{maleimide}$ facial approach is in complete agreement, after the fact, with the stereochemical data. For example, experimentally hydratropaldehyde adds to maleimide providing only one diastereomer (>99:1 d.r.). This fact rules out the possibility of a $Re_{enamine}$, $Si_{maleimide}$ or a $Si_{enamine}$, $Re_{maleimide}$ facial approach, but the enantiomeric ratio, at 96:4, does suggest that the minor enantiomer, (*R*,*S*)-**6h**, may be forming via complex **E** (Figure 3) using the non-competitive steric based approach ($Si_{enamine}$, $Si_{maleimide}$). In summary, the DFT calculations support hydrogen bond preorganization of maleimide at the assembled catalyst, and consequently the origin of the high stereoselectivity of (*S*,*R*)-**6h** can be better appreciated.

With a plausible reaction pathway clarified, it is important to note the mode of hydrogen bonding, catalyst to electrophile, departs from those depicted for non-assembled bifunctional catalysts. For example, the O-*t*Bu-L-Thr, sulfamide, DMAP catalyst system used here employs one resilient hydrogen bond (Figure 2, complex **A**, 1.85 Å) to preorganize the maleimide electrophile to the hydrogen bond donor catalyst site; while non-assembled catalysts, to the best of our knowledge, are depicted as anchoring electrophiles via two critical hydrogen bonds.[34] These divergences are conceivable because sulfamide (Figure 4) is a new hydrogen-bond donor platform, and its structure departs from the traditionally used hydrogen bond donors, for example, ureas and thioureas. For example, in thiourea all atoms are essentially coplanar, see Supporting Information (Computational Sections 2 and 4, respectively, Figures S2 and S4), resulting in a hydrogen bond donor with both NH_2 units in the same plane (Figure 4). By contrast, sulfamide's NH_2 groups are in parallel planes to one another. These geometric realities permit fundamentally different transition states to exist for sulfamide versus thiourea.

In Figure 2, the O-*t*Bu-L-Thr, sulfamide, DMAPcatalyzed reaction is depicted in its four lowest energy complexes. Of note, the diagonal hydrogens of sulfamide always form the two critical (1.78–2.08 Å) hydrogen bonds required to bridge maleimide to the catalyst's carboxylate moiety.[29,35] When O-*t*Bu-L-Thr, thiourea, DMAP, is modeled[36] a different pattern is observed, here the two critical, bridging, hydrogens of thiourea come from the same NH_2 unit (Figure 4, compare thiourea **F** and sulfamide **A** complexes).[37] A closer comparison of these two complexes additionally reveals a threonine conformational difference between the two minima. When sulfamide is present, a linear arrangement of the enamine and carboxylate is preferred, as discussed earlier. The hydrogen bridging required for this conformation of O-*t*Bu-L-Thr is not capable of being replicated by thiourea, based on its preferred hydrogen bonding motif in complex **F** (Figure 4).[36] Finally, it should be noted that a third hydrogen bond is observed for all of the sulfamide and thiourea complexes (Figures 2 and 4), but at 2.31–2.46 Å are expected to play a supportive, but not "anchoring", role.

It was demonstrated experimentally that O-*t*Bu-L-Thr, sulfamide, DMAP, was optimal for nitroalkene additions (Table 1), while this catalyst system was the only useful one for the Mannich reactions (Table 2). By contrast, additions to maleimide electrophiles were faster when using the bicomponent catalyst system of O-*t*Bu-L-Thr, KOH (Table 3, compare entries 11–13). A persuasive argument, for why this might be, is noted when comparing the low energy calculated complexes of Figure 4. For example, under potassium cation activation, complex **G**, the synclinal complex is noteworthy for minimizing the steric repulsion between the maleimide *N*-phenyl and the hydratropaldehyde phenyl moieties (Scheme 3, top complex). A likely consequence is the

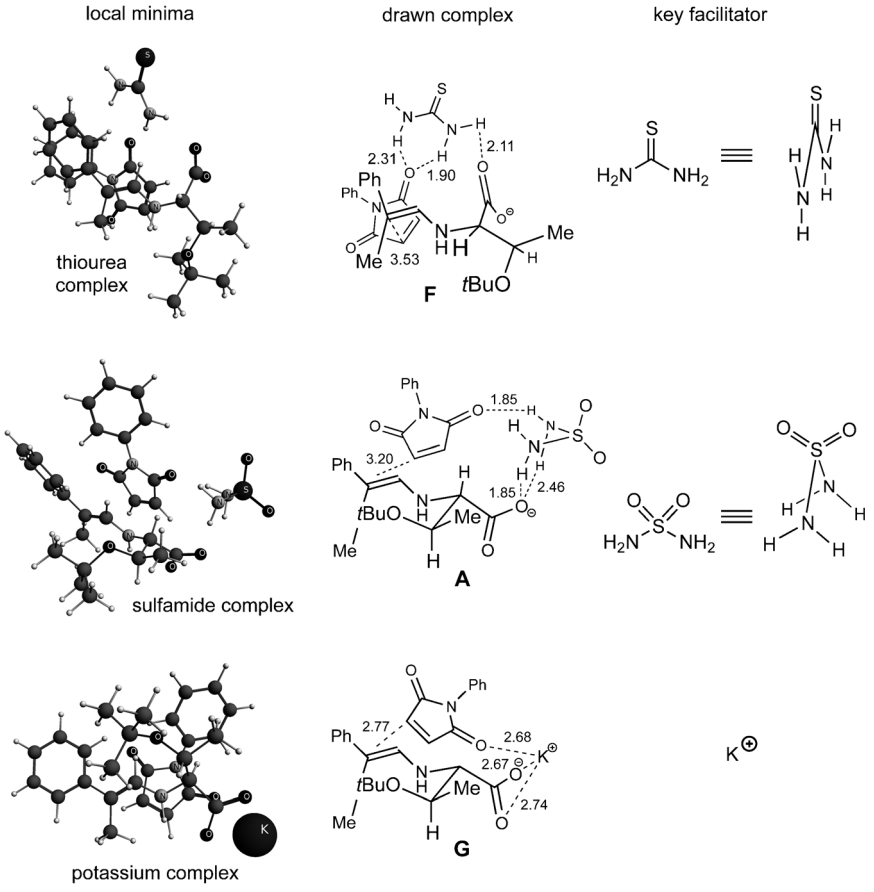


Figure 4. Hydratropaldehyde addition to N-phenylmaleimide: local minima for purely organic vs metal activated catalyst systems.

noted, and significantly shorter, carbon–carbon pre-bond forming distance of 2.77 Å under potassium activation (complex **G**)[38] versus sulfamide activation (3.20 Å, complex **A**, Figure 4 and Scheme 3, bottom complex). The more compact potassium complex may be contributing to the increased rate of reaction (10 h versus 24 h, Table 3 entries 11 and 12). This line of reasoning is perhaps strengthened by the fact that formation of succinimide product **6k** (Table 3) requires the same reaction time for both the bicomponent (entry 18, 4 h) and tricomponent (entry 19, 5 h) catalyst systems. In this instance, the above noted steric interaction (phenyl-on-phenyl for **6h**, Scheme 3, bottom complex) is reduced to phenyl-on-linear alkyl in **6k**. The sulfamide reaction complex, for formation of **6k** (not shown), may consequently have a shortened carbon–carbon pre-bond forming distance that is similar to that found in the corresponding K^+ complex for **6k**. It should be noted that unlike the organic based tricomponent catalyst system calculations, the bicomponent system (potassium cation present) required inclusion of the solvent parameters, in particular, to differentiate the relative energy differences between the *cis* and *trans* enamine complexes, see Supporting Information (Computational Section 5, Figure S5 and Table S20, and General Details of the Computational Section).

These combined results demonstrate the conformational relay effects imposed on the amino acid, sthe assembled catalyst, in the presence of a thiourea based catalyst component (approximately two dimensional) versus a sulfamide catalyst component (three dimensional) versus a potassium cation (spherical), and the consequences on the trajectory of the approaching electrophile. When only considering the maleimide additions, all three catalyst systems enable similar product stereochemistry, albeit via clearly different complexes (Figure 4). These differences alone make it easier to appreciate why different reactions, with dissimilar electrophiles, might favor one of these catalyst systems over the other two. An extreme example is the Mannich reaction (Table 2), where only the mild tricomponent catalyst system of O-*t*Bu-L-Thr, sulfamide, DMAP can be used to catalyze practical product formation. In total, these experimental and computational studies have provided a foundation for how these newly identified catalyst systems might be activating and preorganizing the starting materials. The concept insights gained here can now be leveraged to exploit alternative catalyst components and different reaction types.

Conclusion

The introduction of self-assembled organocatalysts has lagged behind the use of covalently formed organocatalysts, and efficient examples thereof are rare. Here we have provided a new general direction for their further use and exploitation, while simultaneously addressing a challenge in organic synthesis: stereogenic quaternary carbon formation. Tricomponent and bicomponent catalyst systems based on amino acids have been described, with the former requiring the addition of a hydrogen bond donor and DMAP, while the latter only requires the addition of KOH. This flexible catalyst platform, currently only based on commercially available materials, has permitted straight forward reaction fine tuning, unprecedented substrate diversity, and excellent stereoselectivity. For example, O-*t*Bu-L-Thr, sulfamide, DMAP is optimal for nitroalkene Michael reactions, while it is necessary for Mannich product formation. For maleimide

Michael reactions, O-*t*Bu-L-Thr, KOH is optimal because of shortened reaction times. For the DFT calculated maleimide example, we have elaborated on how metal (potassium) cation activation can be replaced by a purely organic compound, for example, sulfamide, via two critical bridging hydrogen bonds. For example, in the lowest energy sulfamide complex (Figure 4, complex **A**), the oxygen$_{maleimide}$···H-N$_{sulfamide}$ hydrogen bond holds maleimide within bonding distance proximity of the enamine by a convincingly strong, lone, hydrogen bond (1.85 Å). This departs from the hydrogen bond preorganization generally espoused for non-assembled catalysts with thioureas, and is perhaps the basis for the exceptional performance of the catalysts noted here. In closing, these results represent the first evidence for the likely reaction pathway enabled by these self-assembled catalysts.

Experimental Section

Extensive details can be found in the Supporting Information, which is divided into three sections: Experimental Section (19 pages of experimental descriptions, 42 pages of HPLC and NMR data), Computational Section (64 pages), and an X-ray Section (4 pages).

CCDC-840712 (**6k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for enantioselective Mannich reactions: To a screw cap vial was added 50 mg of powdered molecular sieves (5 Å), O-*t*Bu-L-Thr (4.4 mg, 0.025 mmol, 5.0 mol%), sulfamide (2.40 mg, 0.025 mmol, 5.0 mol%), and DMAP (3.05 mg, 0.025 mmol, 5.0 mol%). To this mixture was added dichloromethane (1.0 M, 0.50 mL), N-*p*-methoxyphenyl protected α-imino ethyl glyoxylate (1.00 equiv, 0.5 mmol, 103 mg), and the aldehyde (1.2 equiv, 0.6 mmol). This mixture was stirred at room temperature. Once complete, the reactions were quenched by adding water (15 mL) and the resulting mixture was extracted with dichloromethane (3×15 mL). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude reaction mixture, without delay, was purified by column chromatography (EtOAc/pet ether) and the chromatographic and spectroscopic data collected immediately for these semi-labile Mannich products.

General procedure for the enantioselective addition of aldehydes to maleimides: To a screw cap vial was added O-*t*Bu-L-Thr (8.75 mg, 0.05 mmol, 5.0 mol%), sulfamide (4.80 mg, 0.05 mmol, 5.0 mol%), and DMAP (6.10 mg, 0.05 mmol, 5.0 mol%). To this mixture was added CH_2Cl_2 (2.0 M, 0.50 mL) and the aldehyde (1.20 equiv, 1.20 mmol). This mixture was stirred for 2 min at room temperature. N-phenylmaleimide or N-benzylmaleimide (1.00 equiv, 1.00 mmol), was then added and the reaction mixture became homogenous, regardless of the substrate examined. At complete conversion, the reaction mixture was diluted with H_2O (15 mL) and extracted with dichloromethane (3×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed (rotary evaporator). The crude product was purified by column chromatography and the yield obtained.

Acknowledgements

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[21] Except for a lone report on the formation of contiguous quaternary–tertiary stereogenic centers, see Table 3 within ref. [20b], all current reports avoid substrates that produce these products.

[22] For initial solvent screening studies, see the Supporting Information.

[23] It is important to note that the use of O-*t*Bu-L-Thr (5 mol%), Schreiner's thiourea (5 mol%), DMAP (5 mol%), provided a less valuable reaction profile for **6a** (9 h, 92% *ee*, HPLC result).

[24] The best prior result for compound **6h** was: 90% yield, 8:1 d.r., 91% *ee*, after 36 h at 35 °C, when using 20 mol% of a thiourea catalyst and 2.0 equiv of the starting aldehyde, see Table 3 of ref. [20b].

[25] The d.r. measurements before and after silica gel chromatography were consistent, for more details see the Supporting Information.

[26] S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787–1790.

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[29] Three hydrogen bonds are always noted for each complex **A**–**D**, Figure 2, but the third one appears to play an auxiliary role (second hydrogen bond to the carboxylate oxygen is weaker, ranging from 2.32–2.46 Å), perhaps fine tuning the rigidity of the complex initially provided via the two critical, anchoring, hydrogen bonds (1.78–2.08 Å).

[30] When reactants are *not* included, hydrogen-bond donors based on ureas are well known to form two hydrogen bonds, one to each of the carboxylate oxygens. Sulfamide appears to prefer one hydrogen bond, see Supporting Information, Computational Section, compare snapshots in Figure S1 and S2 of Sections 1 and 2. When chemically reactive starting materials are added, e.g., an aldehyde and maleimide, the resulting low energy reaction complexes, for both thiourea and sulfamide, show only one critical (1.78–1.86 Å) hydrogen bond to the carboxylate.

[31] As an aside, complex **E** may be the overwhelmingly preferred low energy complex, in part, because of a secondary stabilizing effect marked by a dipole-dipole attractive force (3.30 Å distance between the β-carbon of the enamine and the indicated electron deficient carbon on the pyridium ring, Figure 3).

[32] T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080.

[33] See the Supporting Information, Computational Section: Discussion A: Steric model considerations (there we explain why the same major product is formed in the absence or presence of sulfamide) and Section 6.

[34] We are unaware of any computational studies modeling the maleimide reactions shown here. For a computational study with a nitroalkene depicting two, critical (<2.2 Å) hydrogen bonds, only to the electrophile (non-assembled catalyst), see: D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826–832.

[35] In Figure 2, seven of the eight critical hydrogen bonds range from 1.78–2.08 Å, the remaining hydrogen bond, at 2.39 Å, is an outlier, it is noted in complex **B**.

[36] Noted in the Supporting Information, but not discussed in the main text, two more low energy thiourea complexes were identified. The 3.88 kcal mol^{-1} higher energy complex used the same hydrogen bonding pattern as the lowest energy complex **F** (Figure 4). The remaining complex, which was 3.16 kcal mol^{-1} higher in energy, was judged to be unlikely to result in product formation (DMAP partially between the reacting starting materials). For snapshots of these complexes see the Supporting Information, Computational Section 4, Figure S4 and Table S16.

[37] Schreiner's thiourea was (experimentally)investigated but proved to be of lower value, for details, see Supporting Information, Computational Section, Discussion B: Computational extrapolations for future research.

[38] The potassium complex in Figure 4 is a low energy island unto itself, the next lowest *trans* enamine potassium complex is 5.33 kcal mol^{-1} higher in energy, while the corresponding lowest energy *cis* enamine potassium complex is 2.87 kcal mol^{-1} higher in energy. The Figure 4 potassium complex, alone, is consequently the only complex that needs to be considered here. See the Supporting Information, Computation Section 5, Figure S5 and Table S20.

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