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Primary Amine-Thioureas with Improved Catalytic Properties for "Difficult" Michael Reactions: Efficient Organocatalytic Syntheses of (*S*)-Baclofen, (*R*)-Baclofen and (*S*)-Phenibut

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Abstract: Among the class of primary amine-thioureas based on *tert*-butyl esters of α-amino acids, the most efficient organocatalyst for "difficult" Michael reactions was identified. The derivative based on (*S*)-di-*tert*-butyl aspartate and (1*R*,2*R*)-diphenylethylenediamine provided the products of the reaction between aryl methyl ketones and nitroolefins in excellent yields and enantioselectivities. In addition, this new catalyst can be used at low catalyst loading (5 mol%). The utility of this methodology was highlighted by the efficient synthesis of (*S*)-baclofen, (*R*)-baclofen and (*S*)-phenibut.

Keywords: amino acids; Michael addition; nitroolefins; organocatalysis; thioureas

Introduction

Organocatalysis now constitutes an established and powerful methodology in asymmetric organic synthesis.[1,2] Although a large number of organic transformations have been accomplished utilizing organocatalysis, there are only three most commonly used modes of activation: enamine activation, iminium ion activation and activation through hydrogen bonding.[3] Molecules that combine a primary amine with a thiourea functionality have emerged as very powerful organocatalysts.[4] One of the key organic transformations that is catalyzed by this class of organocatalysts is the "difficult" Michael reaction between aromatic ketones and nitroolefins, since the asymmetric Michael reaction constitutes one of the most important processes for the synthesis of new C–C and C–X bonds.[5,6] However, only few examples of chiral thioureas containing a primary amino group have been reported to catalyze efficiently the Michael reaction between aromatic ketones and nitroolefins. Jacobsen's thiourea **1** (Figure 1),[7] Tsogoeva's thiourea **2**,[8] Ma's thiourea **3** based on sacharide[9] and thiourea **4** developed by Xu and co-workers[10] were among the most succesful examples, along with thiourea **5** developed by us (Figure 3).[11] In the present work, we would like to present our recent findings on the study of the structural features that are required in the catalyst's structure in order to possess increased reactivity and deliver increased selectivities.

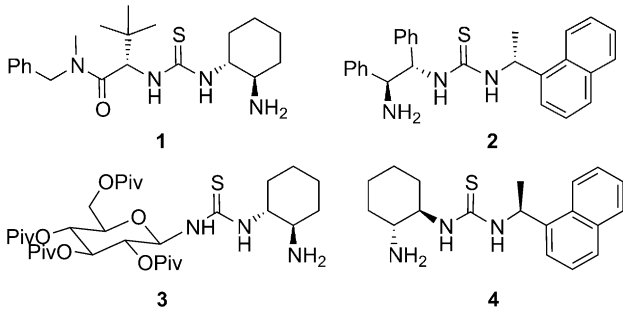


Figure 1. Efficient organocatalysts for "difficult" Michael reactions.

Results and Discussion

The mode of dual activation by a thiourea organocatalyst is illustrated in Figure 2. Based on our previous experience in organocatalysis,[12] we showed that two chiral building units on a thiourea are necessary in order that a catalyst can present high reactivity.[11,13] In our earlier study,[11] the 1,2-diphenylethylene moiety and the bulky chiral backbone of an α-amino acid were found to meet these criteria. However, when more than one asymmetric center coexists in

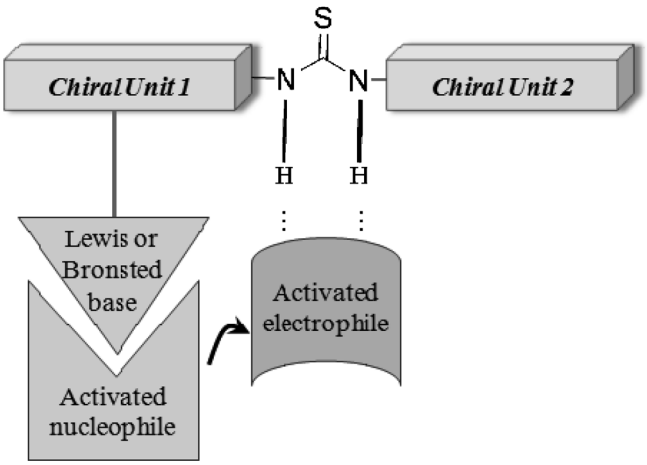


Figure 2. Dual activation of nucleophile and electrophile by an organocatalyst.

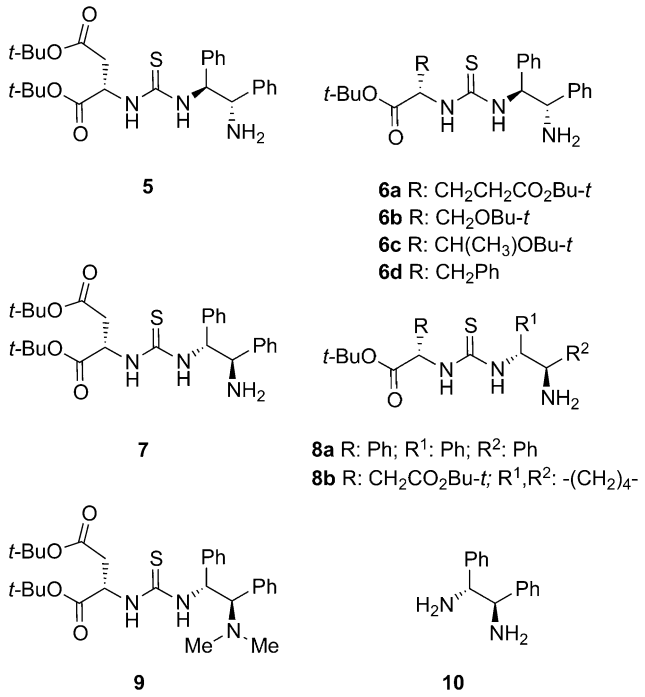
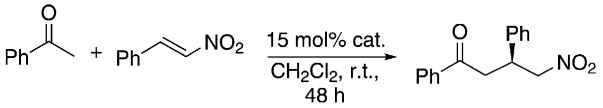


Figure 3. Organocatalysts utilized in this study.

the chiral units of the catalyst, a careful study of "match" and "mis-match" effects is necessary in order to identify the optimum combination of the configuration of stereogenic centers, which leads to optimum catalytic properties. Among the α-amino acids utilized, (some of them, **5** and **6a–d** are depicted in Figure 3), catalyst **5** based on di-*tert*-butyl aspartate provided the best results (entry 1 *vs.* entries 2–5 in Table 1).[11] Although catalyst **5** provided the desired product in a good yield (68%) and the enantioselectivity was high (95% *ee*), an improvement was still needed. Upon replacing the (1*S*,2*S*)-diphenylethylenediamine by (1*R*,2*R*)- diphenylethylenediamine, a quantitative yield and excellent selectivity were observed (entry 6, Table 1). Directly attaching a phenyl group instead of the aspartic acid side chain led to slightly worse results (entry 7, Table 1). When the diphenylethylene moiety was replaced by the cyclohexyl group, the *ee* remained high but the yield dropped significantly (entry 8, Table 1). In order to prove that both primary amine functionality and thiourea moiety are required for the excellent catalytic reactivity, a tertiary amine-thiourea **9** corresponding to the optimum catalyst **7** as well as (1*R*,2*R*)-diphenylethylenediamine **10** were utilized as catalysts, however, no reaction took place (entries 9 and 10, Table 1). The enantiomer of **7** was also synthesized leading to the other enantiomer of the product in high yield and enantioselectivity (entry 11, Table 1).

Table 1. Michael reaction between acetophenone and *trans*-β-nitrostyrene using various catalysts under the previously optimized conditions.[a]

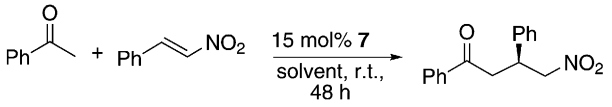


Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**5**[d]	68	−95
2	**6a**[d]	32	−77
3	**6b**[d]	51	−95
4	**6c**[d]	27	−96
5	**6d**[d]	37	−92
6	**7**	100	99
7	**8a**	98	98
8	**8b**	22	96
9	**9**	–	–
10	**10**	–	–
11	**7**-ent	71	-99

[a] *Reaction conditions:* catalyst (0.03 mmol), *trans*-β-nitrostyrene (0.20 mmol) and acetophenone (2.00 mmol) in CH_2Cl_2 (1.0 mL).
[b] Isolated yield.
[c] The enantiomeric excess (*ee*) was determined by chiral HPLC.
[d] Data from ref.[11]

Once the optimum catalyst was found, a screening of the various reaction conditions took place (Table 2). Chlorinated solvents and non-polar solvents provided the best results (entries 1–8, Table 2). $CHCl_3$ afforded the product in quantitative yield and excellent enantioselectivity (entry 2, Table 2), while the results obtained in water are noteworthy (entry 8, Table 2). Acid additives seem not to have an influence on the reaction outcome, although if water is also added lower yields are obtained (entries 9–11, Table 2). The reaction can be performed at elevated temperature and the ketone:nitrooelfin ratio can be

Table 2. Michael reaction between acetophenone and *trans*-β-nitrostyrene using catalyst **7**.[a]

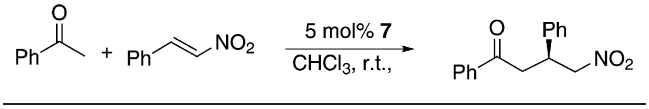


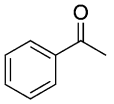
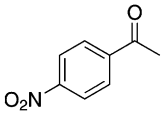
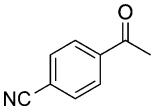
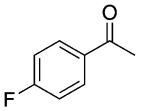
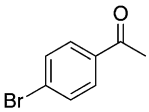
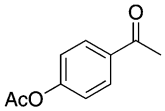
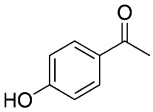
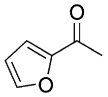
Entry	Conditions	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	100	>99
2	$CHCl_3$	100	>99
3	toluene	98	>99
4	Et_2O	67	99
5	THF	–	–
6	EtOAc	65	>99
7	DMSO	–	–
8	H_2O	85	>99
9	$CHCl_3$, PhCOOH	100	>99
10	$CHCl_3$, 4-NBA	100	>99
11	$CHCl_3$, PhCOOH, H_2O	90	>99
12[d]	$CHCl_3$	100	>99
13[e]	$CHCl_3$	59[f]	>99
14[d,g]	$CHCl_3$	100	99
15[d,h]	$CHCl_3$	98	>99
16[d,i]	$CHCl_3$	96	>99

[a] *Reaction conditions:* catalyst (0.03 mmol), *trans*-β-nitrostyrene (0.20 mmol) and acetophenone (2.00 mmol) in CH_2Cl_2 (1.0 mL).
[b] Isolated yield.
[c] The enantiomeric excess (*ee*) was determined by chiral HPLC.
[d] Ketone:nitrostyrene 5:1.
[e] Ketone:nitrostyrene 2:1.
[f] The reaction reaches completion after 96 h.
[g] Reaction took place at 80 °C in a pressure vessel.
[h] 10 mol% catalyst was used.
[i] 5 mol% catalyst was used.

reduced with no significant loss in either the yield or the selectivity (entries 12 and 14, Table 2). When the ratio of ketone:nitrostyrene is reduced to 2:1, the reaction is slower and needs prolonged reaction time to reach completion (entry 13, Table 2). Furthermore, the catalyst loading can be significantly reduced to 5 mol% (entry 16, Table 2). The scope and limitations of the present methodology were also explored. A variety of substituted aromatic methyl ketones was successfully used under this protocol (Table 3). Electron-withdrawing groups, such as *p*-nitro and *p*-cyano, furnished the desired product in high yields and excellent enantioselectivities (entries 2 and 3, Table 3). Halogen substituents such as *p*-fluoro and *p*-bromo, led also to high yields, although they required either higher catalyst loading (entry 4, Table 3), or longer reaction time (entry 5, Table 3). *p*-Acetoxyacetophenone and *p*-hydroxyacetophenone were also well tolerated (entries 6 and 7, Table 3), while heterocyclic aromatic moieties, like furyl, led to quantitative yield and high selectivity (entry 8, Table 3).

Table 3. Michael reaction between aryl methyl ketones and *trans*-β-nitrostyrene using catalyst **7**.[a]



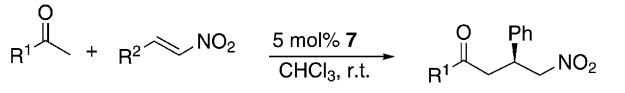
Entry	Ketone	Reaction time [h]	Yield [%][b]	*ee* [%][c]
1		48	96	>99
2		72	80	>99
3		72	89	99
4[d]		72	73	>99
5		96	74	>99
6		72	82	99
7[d]		72	84	98
8		72	85	99

[a] *Reaction conditions:* catalyst (0.01 mmol), *trans*-β-nitrostyrene (0.20 mmol) and acetophenone (1.00 mmol) in $CHCl_3$ (1.0 mL).
[b] Isolated yield.
[c] The enantiomeric excess (*ee*) was determined by chiral HPLC.
[d] 10 mol% catalyst was used.

To further demonstrate the high enantiocontrol and reactivity that is provided by our new catalyst, a variety of substituted nitroolefins was used in the reaction with either acetophenone or acetone (Table 4). It is well established that such reactions suffer from decreased yields in the case of acetophenone and low enantioselectivities in the case of acetone.

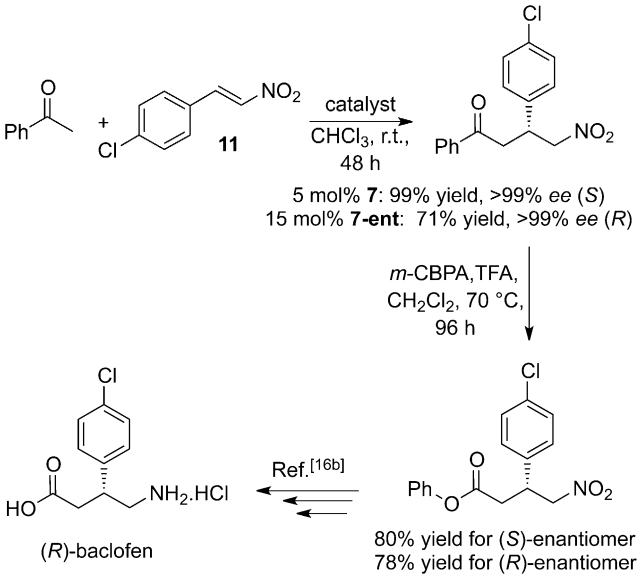
Like acetophenone, acetone afforded the product in quantitative yield and excellent enantioselectivity (entries 1 and 2, Table 4). In some cases, when acetone was employed, the yield was lower due to the formation of the double Michael product. In order to

Table 4. Michael reaction between ketones and nitroolefins using catalyst **7**.[a]



Entry	R^1	R^2	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	48	96	>99
2[d,e]	Me	Ph	48	96	99
3	Ph	4-$MeOC_6H_4$	72	98	>99
4[d,e]	Me	4-$MeOC_6H_4$	72	91	99
5	Ph	4-$NO_2C_6H_4$	48	96	99
6[d]	Me	4-$NO_2C_6H_4$	48	85	94
7	Ph	4-FC_6H_4	48	99	>99
8	Me	4-FC_6H_4	24	91	>99
9	Ph	4-ClC_6H_4	48	99	>99
10[d,e]	Me	4-ClC_6H_4	48	92	98
11	Ph	2-furyl	72	87	99
12	Me	2-furyl	24	99	>99
13	Ph	3-$NO_2C_6H_4$	96	82	99
14[d]	Me	3-$NO_2C_6H_4$	72	94	98
15	Ph	2-$NO_2C_6H_4$	96	79	>99
16[f]	Ph	2-$NO_2C_6H_4$	24	76	99
17[d]	Me	2-$NO_2C_6H_4$	72	96	99

[a] *Reaction conditions:* catalyst (0.01 mmol), nitroolefin (0.20 mmol) and ketone (1.00 mmol) in $CHCl_3$ (1.0 mL).
[b] Isolated yield.
[c] The enantiomeric excess (*ee*) was determined by chiral HPLC.
[d] 10 mol% AcOH was used.
[e] 10 mol% catalyst was used.
[f] The reaction took place at 80 °C in a pressure vessel.



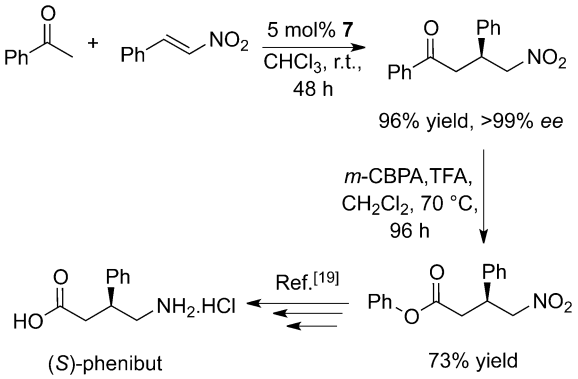
Scheme 1. Organocatalyzted synthesis of (*S*)- and (*R*)-baclofen.

avoid this side reaction, AcOH was added to the reaction mixture. When electron-donating substituents were used, like *p*-methoxy, high yields can be obtained in both the cases of acetophenone and acetone, accompanied by high enantioselectivities (entries 3 and 4, Table 4). The use of electron-withdrawing substituents on the nitroolefin afforded the desired product in good to high yields and always in high enantioselectivities (entries 5–10, Table 4). Finally, nitroolefins bearing heterocycles like furyl, were also well tolerated (entries 11 and 12, Table 4). In order to expand the breadth of the substrate scope, *meta*- and *ortho*-substituted nitroolefins were employed (entries 13–17, Table 4). Excellent yields and selectivities were obtained, albeit in some cases prolonged reaction times were needed. It has to be highlighted that these prolonged reaction times could be reduced, if the reaction took place in a pressure vessel at 80 °C, without any significant loss of the enantioselectivity (entry 16, Table 4).

The importance of this methodology is highlighted in the efficient synthesis of (*S*)- and (*R*)-baclofen (Scheme 1). Baclofen is an analogue of the neurotransmitter γ-aminobutyric acid which is used therapeutically to treat spasticity caused by spinal cord injury or various neurological disorders.[14] The (*R*)-enantiomer is an agonist of the $GABA_B$ receptor, while the (*S*)-enantiomer is essentially inactive.[15] Various syntheses starting from commercially available chiral materials or involving resolutions or syntheses based on biocatalytic transformations have been reported.[16] The key-step involves the enantioselective organocatalytic Michael addition between acetophenone and nitroolefin **11**. The use of primary amine thiourea **7** at 5 mol% catalyst loading delivered the Michael product in quantitative yield and excellent enantioselectivity. Using **7**-ent the opposite enantiomer was obtained in 71% yield and excellent enantioselectivity. Bayer–Villiger oxidation gave rise to a substituted γ-nitro ester that can be transformed in two steps into the desired (*R*)- or (*S*)-baclofen according to published procedures.[16b] Another related GABA-mimetic psychotropic drug, which is clinically used is phenibut.[17] Again, one of the two enantiomers is the biologically active one.[18] Using the model reaction, the Michael product was delivered in excellent yield and selectivity (Scheme 2). Bayer–Villiger oxidation provided the corresponding γ-nitro ester that can furnish enantiopure phenibut by reported procedures.[19]

In order to account for the excellent stereoselectivity of the reaction, the following transition state is proposed (Figure 4). The primary amine of the catalyst activates the aromatic ketone through the formation of an enamine. Unlike the enamine formed by a secondary amine, no secondary destabilizing interactions are encountered.

Simultaneously to the ketone activation, the hydrogen bonding between the thiourea moiety of the cata-



Scheme 2. Organocatalyzed synthesis of *(S)*-phenibut.

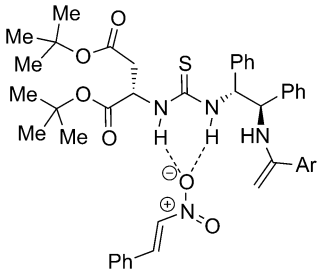


Figure 4. Proposed transition state of the Michael addition of aryl methyl ketones to nitroolefins.

lyst and the nitro group of the nitrostyrene is responsible for the electrophile activation, which guides the Michael addition just from the one face leading to high enantiocontrol.

The structures of catalysts **5** and **7** were minimized using Maestro 9.1 Macromodel (see Supporting Information). The primary amine functionality of catalyst **5** is placed above the plane of the thiourea (Figure 5, A), while the primary amine functionality of catalyst **7** is placed below the plane of the thiourea (Figure 5, B). Thus, it is clear that the configuration of the diamine governs which enantiomer of the product is produced leading in the case of catalyst **5** to (*R*)-enantiomer product and in the case of catalyst **7** to (*S*)-enantiomer. The minimized energy conformation of

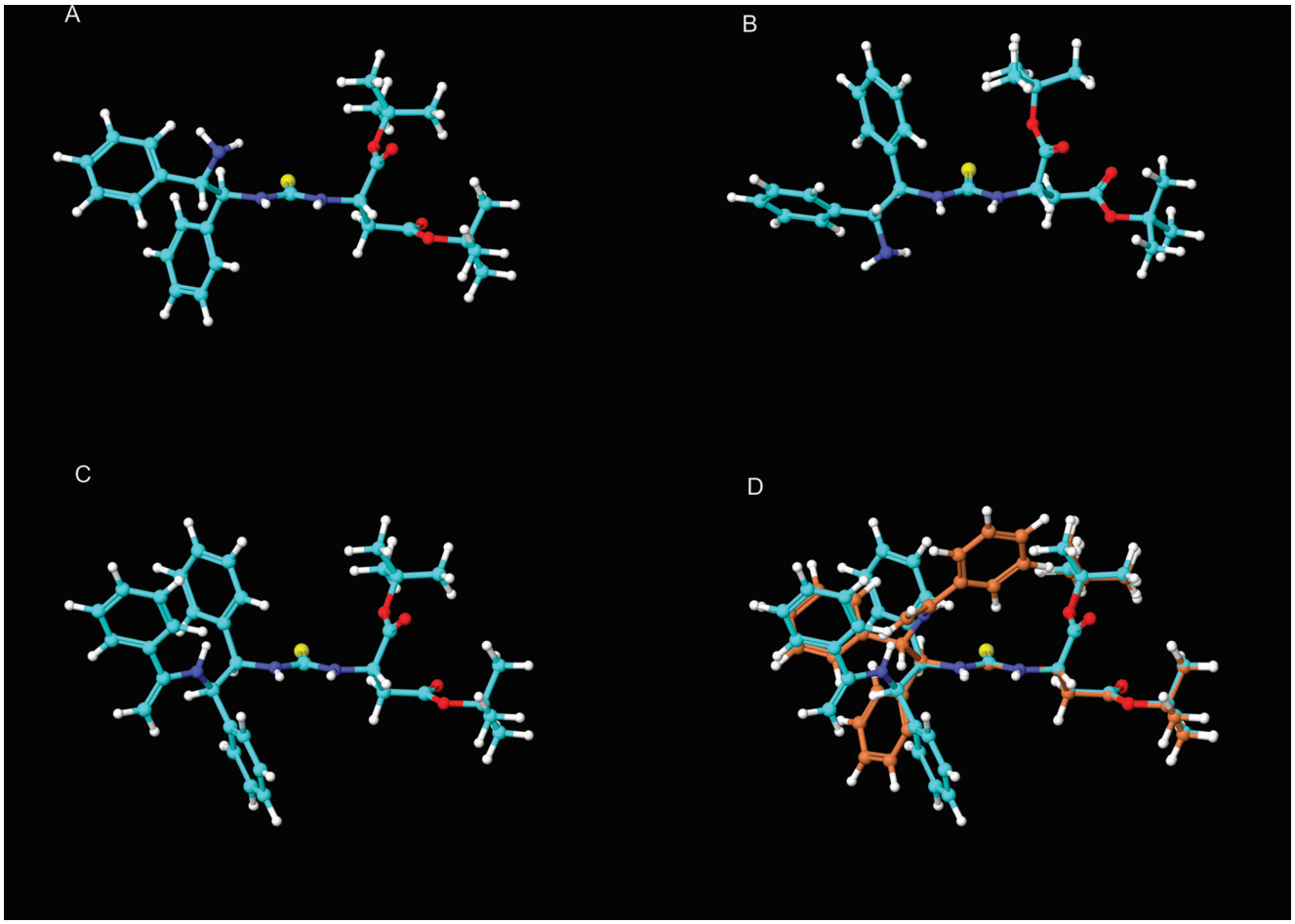


Figure 5. Minimized energy conformations of: (A) catalyst **5**, (B) catalyst **7**, (C) intermediate enamine of catalyst **7** and (D) superimposition of intermediate enamines of catalysts **5** and **7**.

the proposed intermediate enamine of catalyst **7** with acetophenone as well as the superimposition of enamines of catalysts **5** and **7** are illustrated in Figure 5, C and D, respectively. In the case of enamine of catalyst **7**, the phenyl ring of the (1*R*,2*R*)-diphenylethylenediamine backbone seems to block efficiently the left side of the thiourea moiety. It could be assumed that this conformation locks the orientation of the nitroolefin in such a way that the aryl group of the nitroolefin is away from the phenyl group of the diamine, thus leading to higher levels of enantio-induction. In the enamine of catalyst **5**, the same phenyl group from the catalyst's backbone seems to be far away, thus not being able to produce such an efficient blocking of the space, delivering lower levels of selectivity.

Conclusions

In conclusion, we have demonstrated that an easily synthesized and low-cost primary amine-thiourea based on (1*R*,2*R*)-1,2-diphenylethylenediamine and (*S*)-di-*tert*-butyl aspartate is an excellent catalyst for the "difficult" Michael reaction between aryl methyl ketones and nitroolefins. The new catalyst may work at low catalyst loading (5 mol%) providing the products in high to excellent yields and excellent enantioselectivities. The utility of this methodology was highlighted in the efficient synthesis of (*S*)- and (*R*)-baclofen and (*S*)-phenibut.

Experimental Section

General Procedure for the Michael Reaction of Ketones with Nitroolefins

A solution of catalyst **7** (5 mg, 0.01 mmol), nitroolefin (0.2 mmol) and ketone (1 mmol) in chloroform (1 mL) was stirred for the stated time. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with the appropriate mixture of petroleum ether (40–60 °C)/EtOAc to afford the desired product.

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