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Enantioselective Organocatalytic Direct Michael Addition of Nitroalkanes to Nitroalkenes Promoted by a Unique Bifunctional DMAP-Thiourea

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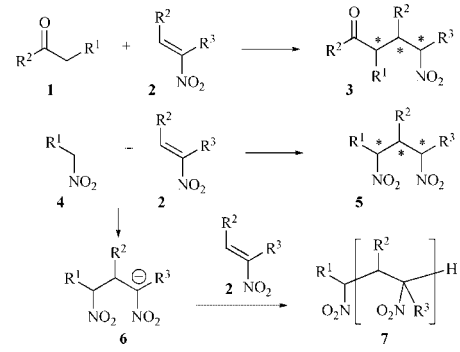
Conjugate addition to nitroalkenes is a versatile reaction that benefits from the high reactivity of nitroalkenes.[1,2] The Michael addition of carbonyl compounds to nitroalkenes is valued for its ability to generate γ-nitro carbonyl compounds of the type **3** which can serve as precursors to γ-amino carbonyl compounds upon reduction or 1,4-dicarbonyl compounds via a Nef reaction (Scheme 1). The first report of an asymmetric catalyst for this reaction appeared in 1996 and involved a chiral base derived from a cinchona alkaloid.[3] Since, the catalytic asymmetric addition of carbonyls to nitroalkenes has been the subject of intense scrutiny by the chemical community. Cumulative efforts of work appearing in 112 publications have led to the identification of several highly tuned and refined catalysts.[2,4]

In contrast, only four reports describe efforts to develop chiral catalysts for the asymmetric catalytic Michael addition of nitroalkanes to nitroalkenes.[5] One is not a direct Michael addition since it requires preformed silyl nitronates.[5a] Two involve organometallic catalysts which are Ti/Zn[5b] and La[5d] based. The fourth involves a modified cinchona alkaloid as an organocatalyst, but the reactions are quite sluggish and require 6−12 d to achieve 10 turnovers.[5c] This dearth of reports on the Michael addition of nitroalkanes to nitroalkenes is surprising since 1,3-dinitro compounds of the type **5** would be a convenient source of 1,3-diamines (Scheme 1). One reason for this may be related to the fact that the nitronate anion **6** is very prone to subsequent addition of nitroalkene leading to oligiomers of the type **7**.[6] As a result this reaction has been difficult to catalyze, and to the best of our knowledge there is only one example of a reaction that has been effected with a substoichiometric amount of a nonchiral catalyst.[7] Recently, we have found that as little as 2 mol% of a simple nonchiral thiourea can accelerate this reaction while suppressing oligomer formation.[8] Herein, we report on the development of a highly enantioselective version of this reaction using a novel bifunctional thiourea catalyst that was rationally designed for this particular transformation.

We focused our investigations on the design of a bifunctional catalyst that would incorporate both a thiourea moiety and base. 2,2′-Diamino-1,1′-binaphthyl (BINAM) was chosen as the chiral scaffold whose conjugates with thioureas[9] have been relatively unexplored. Wang and co-workers developed the BINAM bifunctional thiourea **8** (Figure 1) as an asymmetric catalyst for the Morita−Baylis−Hillman reaction,[10] and subsequently this catalyst has been found useful in the asymmetric Michael addition of 1,3-dicarbonyls to nitroalkenes.[11] The same group has investigated **8** as a catalyst for the Michael addition of nitroalkanes to nitroalkenes but found it to be a very sluggish catalyst.[5c] They found that the reaction of *trans*-nitrostyrene with 2-nitropropane only gave a 29% yield after 48 h for a reaction carried out neat with 10 mol% of **8**. We reasoned that catalyst **9** may have an increased efficiency for this reaction for two reasons. The dimethylamino-pyridine (DMAP) unit in **9** should be much more basic[12] than the dimethylaryl-amine function in **8** leading to more efficient deprotonation of the nitroalkane,

Scheme 1



and once deprotonated, the nitronate anion of the resulting ion pair should be able to noncovalently interact with the protonated DMAP via two hydrogen bonds (Figure 1). We envisioned that it may be possible for a catalyst such as **9** to interact via both components via double H-bonds, bringing them into close proximity in the chiral pocket and thereby influencing both the reactivity and selectivity of the reaction. While chiral catalysts containing the DMAP unit are well-known for a variety of reactions,[13] especially the resolution of alcohols, there is only one example for a Michael addition reaction. Kotsuki reported that a DMAP−pyrrolidine hybrid was effective for the Michael addition of ketones to nitroalkenes.[14] In addition to chiral DMAP catalysts, there are other related 2-aminopyridine catalysts that have been reported.[15] The chiral DMAP−thiourea hybrid (*R*)-**9** can be readily prepared in two steps from the commercially available 2,2′-diamino-1,1′-binaphthyl (*R*)-**10** in two steps (Scheme 2).

An initial screen of the bifunctional catalyst (*R*)-**10** for the Michael addition of nitroalkanes to nitroalkenes was quite encouraging. All of the reactions in Table 1 produced only small amounts of polymer or oligiomers which can be the exclusive product when substoichiometric amounts of a base is used as catalyst.[8,16] Since catalyst **8** is sluggish for this reaction under neat conditions,[5c] it was not surprising to find that it is even more sluggish when a solvent is used (entry 1). To optimize turnover, the reaction of 1-nitropropane and nitrostyrene was investigated with decreasing amounts of the catalyst (*R*)-**9**, and as expected, the rate of the reaction decreased with decreasing amounts of the catalyst. However, the increase in asymmetric induction (and the dr) with lower catalyst loading was surprising. The optimal catalyst loading with regard to asymmetric induction is 0.5−2 mol% although the reactions are too slow under these conditions to be useful. Nonetheless, at these low catalyst loadings, the reactions are extremely clean by ^{1}H NMR revealing only starting material and product with little or no evidence of polymer formation.

Further optimization lead to conditions that allowed the use of only 2 mol% catalyst and which gave high yields and excellent asymmetric inductions for a variety of substrates (Table 2). For example the reaction of 1-nitropropane (**12a**) with nitrostyrene (**13**)

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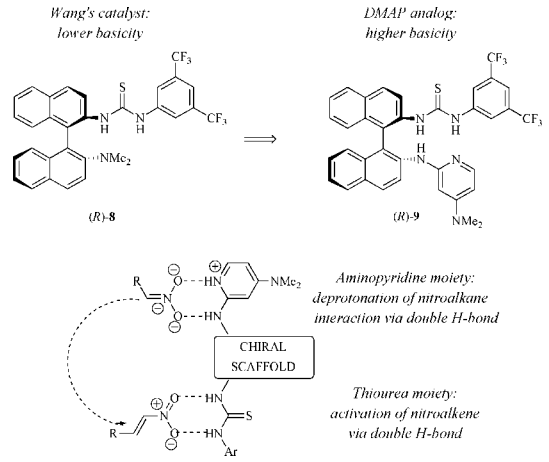


Figure 1. Design of a new bifunctional thiourea/DAMP catalyst for nitro-group activation.

Scheme 2

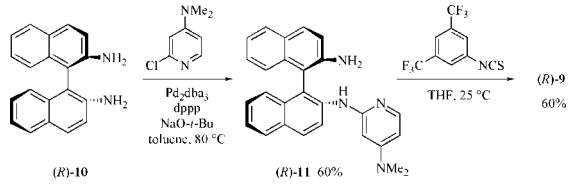
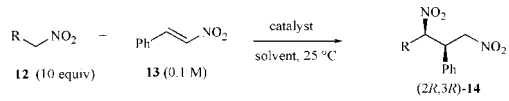


Table 1. Preliminary Screen with Nitroalkanes and Nitrostyrene[a]



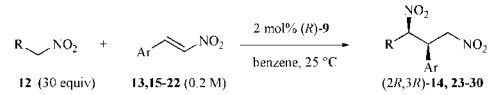
entry	R[b]	catalyst	cat (mol%)	solvent	% yield[c]	syn:anti	% ee syn	% ee anti
1	Et	**8**	20	CH_2Cl_2	0	–	–	–
2	Et	**9**	20	CH_2Cl_2	90	59:41	78	nd
3	Et	**9**	100	benzene	60	39:61	70	63
4	Et	**9**	20	benzene	80	60:40	82	70
5	Et	**9**	10	benzene	40	71:29	84	60
6	Et	**9**	5	benzene	70	76:24	90	70
7	Et	**9**	2	benzene	43	82:18	94	nd
8	Et	**9**	1	benzene	<30	87:13	94	nd
9	Et	**9**	0.5	benzene	18[d]	86:14	95	nd
10	Me	**9**	10	benzene	100	57:43	62	60
11	*n*-Pr	**9**	20	benzene	96	55:45	81	79

[a] Unless otherwise specified, all reactions were run at 0.1 M in **13** with 10 equiv of **12** and with either (*R*)-**8** or (*R*)-**9** as catalyst at 25 °C for 12−15 h. nd = not determined. Entries 5−9 did not go to completion. [b] **12a** R = Et, **12b** R = Me, **12c** R = *n*-Pr. [c] Determined by ^{1}H NMR with triphenylmethane as internal standard. [d] Reaction time was 40 h.

went to completion when the concentration was increased to 0.2 M, the amount of excess nitroalkane was increased to 30 equiv, and the reaction time extended to 40 h (entry 1, Table 2 vs entry 7, Table 1). With these conditions, excellent enantioselectivities were observed over a range of electron-rich and -poor nitrostyrenes including those that are *ortho*-substituted.[17]

In summary, a new catalyst has been developed that will effect the Michael addition of nitroalkanes to nitroalkenes with excellent asymmetric inductions (91−95% ee). Remarkably, the asymmetric induction increases with decreasing catalyst loading with the optimal compromise between rate and induction at a loading of 2 mol%. The obdurate nature of this reaction has made attempts at its acceleration a formidable challenge. The successful catalyst design described herein should find applications in other reactions requiring bifunctional catalysts with both H-bond donors and a Brønsted base.

Table 2. Michael Addition of Nitroalkanes to Nitroalkenes with Catalyst (*R*)-**9**[a]



entry	R[b]	nitroalkene	Ar	Adduct	% yield[c]	syn:anti[d]	% ee syn
1	Et	**13**	Ph	**14a**	80	84:16	95
2	Et	**15**	4-$MeOC_6H_4$	**23**	60	85:15	94
3	Et	**16**	2-$MeOC_6H_4$	**24**	55	80:20	94
4	Et	**16**	2-$MeOC_6H_4$	**24**	94[e]	80:20	94
5	Et	**17**	4-MeC_6H_4	**25**	72	81:19	94
6	Et	**18**	2-ClC_6H_4	**26**	84	74:26	92
7	Et	**19**	4-ClC_6H_4	**27**	75[f]	83:17	92
8	Et	**20**	4-BrC_6H_4	**28**	75[f]	87:13	93
9	Et	**21**	3-BrC_6H_4	**29**	69	90:10	94
10	Et	**22**	2-BrC_6H_4	**30**	78	74:26	92
11	*n*-Pr	**13**	Ph	**14c**	78	90:10	91

[a] Unless otherwise specified, all reactions were run at 0.2 M in nitroalkene with 30 equiv of **12** and 2 mol% of catalyst (*R*)-**9** for 40 h. [b] **12a** R = Et, **12c** R = *n*-Pr. [c] Combined isolated yields of syn and anti isomers after silica gel chromatography. [d] Calculated from the weights of the separated diastereomers except entries 1−4 which were determined by ^{1}H NMR on the crude reaction mixture. [e] Reaction time was 60 h, and the concentration of nitroalkene was 0.33 M. [f] Reaction time was 17 h.

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Supporting Information Available: Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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