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Cyclohexane-1,2-diamines: Efficient Catalysts for the Enantioselective Conjugate Addition of Ketones to Nitro Olefins

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Simple monosulfonated cyclohexane-1,2-diamines are highly enantioselective organocatalysts for the conjugate addition of ketones to nitro olefins. By focusing on aromatic ketones as the most challenging substrates, selectivities of up to 98 % *ee* can be achieved for the title reaction. Moreover, a three-component process between the primary amine catalyst, the nitroalkene, and the ketone, which results in the irreversible formation of pyrrols has been recognized as a reaction pathway for catalyst deactivation.

Introduction

Conjugate addition reactions of aldehydes and ketones to nitro olefins promoted by organocatalysts have been extensively studied.[1,2] While secondary amines such as proline give good results with aldehydes and cyclic ketones as substrates, acyclic ketones have proved to be more difficult substrates.[3–7] For the latter, thiourea catalysts, flanked on both sides with chiral directing groups and bearing, in addition, a primary amino group[8–10] such as **1**[8] and **2**,[9] have been successfully developed (Figure 1). In general, primary amines are increasingly recognized as powerful organocatalysts.[11,12]

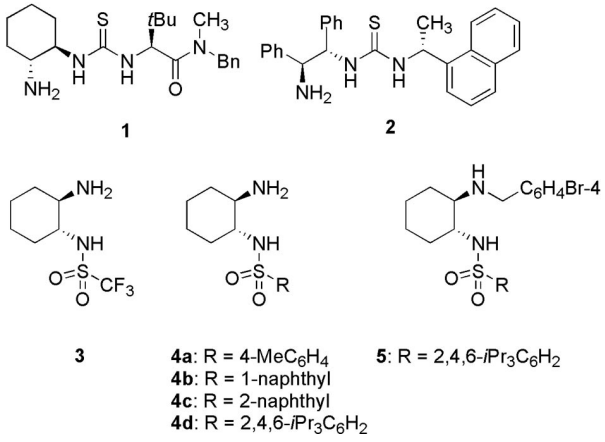

Figure 1. Organocatalysts for the conjugate addition of carbonyl compounds to nitroalkenes.

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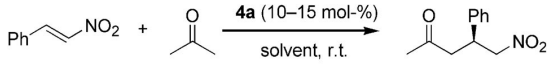
Very recently, the simple diamine **3** was reported in an elegant study to be effective in catalyzing the addition of acyclic methyl ketones to nitroalkenes in up to 87% *ee*,[13] which prompted us to disclose our own study. Focusing especially on aromatic methyl ketones as the more challenging substrates, we wish to disclose **4d**[14] as an effective catalyst that gives rise to selectivities of up to 98% *ee* for the title transformation and to provide some insight into the mechanism by identifying a reaction pathway that causes catalyst deactivation.

Results and Discussion

We began our study by screening catalyst **4a** for the addition of acetone (**7a**) to β-nitrostyrene (**6a**) in different solvents (Table 1) and suggest that toluene is the most suitable with respect to yields and selectivity to give rise to **8a** (80% yield, 73% *ee*, Entry 8). The use of additives, which proved to be successful with other catalysts for this transformation,[9,15–22] did not lead to further improvement (Entries 9 and 10). Under solvent-free conditions, equimolar amounts of benzoic acid seem to be beneficial in terms of enantioselectivity (Entries 5 and 6); however, the results that were achieved under the latter conditions were inferior with respect to yield.

By varying the aromatic group of the sulfonamide in **4**, the isopropyl-substituted derivative **4d** was found to significantly improve the enantioselectivity of **8a** to 87% *ee*, and by using 20 mol-% of this catalyst, quantitative conversion was achieved (Table 2, Entry 4). Further attempts to optimize the results by screening additives for this catalyst, however, were again unsuccessful. While acceleration of the rate of reaction occurs in the presence of protic additives, an undesirable decrease in enantioselectivity was observed (Entries 5–12).

Table 1. Conjugate addition of acetone to β-nitrostyrene with **4a**.

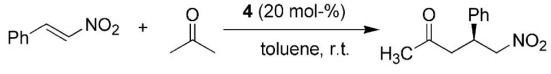


6a **7a** **8a**

Entry	Loading(**4a**) [mol-%]	Solvent	Additive[a]	Yield [%]	*ee* [%][b]
1	10	EtOH	–	29	26
2	10	CH_2Cl_2	–	51	62
3	10	hexane	–	0	–
4	10	THF	–	43	33
5	15	neat	–	82	32
6	15	neat	PhCOOH	68	71
7	15	neat	H_2O, AcOH	84	58
8	15	toluene	–	80	73
9	15	toluene	PhCOOH	44	62
10	15	toluene	H_2O, AcOH	58	61

[a] Equimolar amounts with respect to catalyst **4a** were employed. [b] Determined by HPLC (Chiralpak AS-H); the configuration of **8a** was assigned by comparing optical rotation data and HPLC retention times with literature data.[8–10]

Table 2. Screening of catalysts **4**.



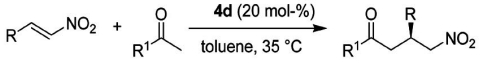
6a **7a** **8a**

Entry	Catalyst	Time [h]	Additive (mol-%)	Yield [%][a]	*ee* [%][b]
1	**4a**	62	–	96	73
2	**4b**	62	–	88	74
3	**4c**	44	–	86	70
4	**4d**	62	–	98	87
5	**4d**	10	PhCOOH (10)	92	64
6	**4d**	60	PhCOOH (20)	35	82
7	**4d**	70	AcOH (10)	79	85
8	**4d**	60	AcOH (20)	57	74
9	**4d**	70	4 Å MS	84	58
10	**4d**	48	$MgSO_4$	97	82
11	**4d**	48	H_2O (1000)	99	76
12	**4d**	70	H_2O (20)	62	75

[a] Isolated yield. [b] The *ee* values were determined by HPLC (Chiralpak AS-H).

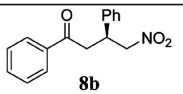
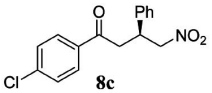
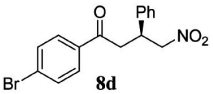
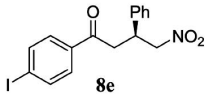
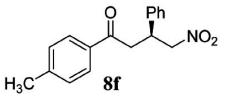
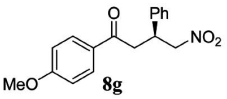
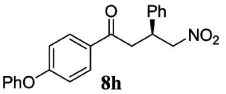
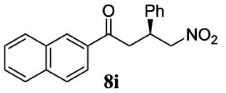
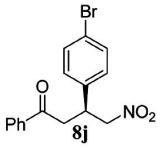
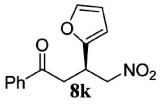
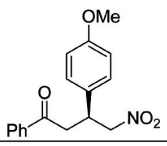
Turning to the more challenging aromatic ketones, we were pleased to note that with catalyst **4d** enantioselectivities of up to 98% *ee* were achieved; however, as expected these substrates turned out to be less reactive (Table 3). Raising of the reaction temperature to 35 °C was found to give improved yield, whilst retaining the high selectivities observed at 20 °C, but even higher temperatures were not tolerated well (Entries 1–4). Under the optimized conditions, **8b**–**8k** were obtained in 94–98% *ee* with acceptable yields (Entries 2, 5–13). Besides β-nitrostyrene (**6a**), the *p*-bromophenyl and the 2-furyl analogs **6b** and **6c**, respectively, could be employed as nitroalkenes, while the more electron-rich *p*-methoxyphenyl derivative **6d** proved to be not reactive enough to undergo the conjugate addition reaction (Entries 12–14).

Table 3. Conjugate addition of aromatic ketones to β-nitrostyrenes with **4d**.



6a: R = Ph
6b: R = 4-BrC_6H_4
6c: R = 2-furyl
6d: R = 4-$MeOC_6H_4$

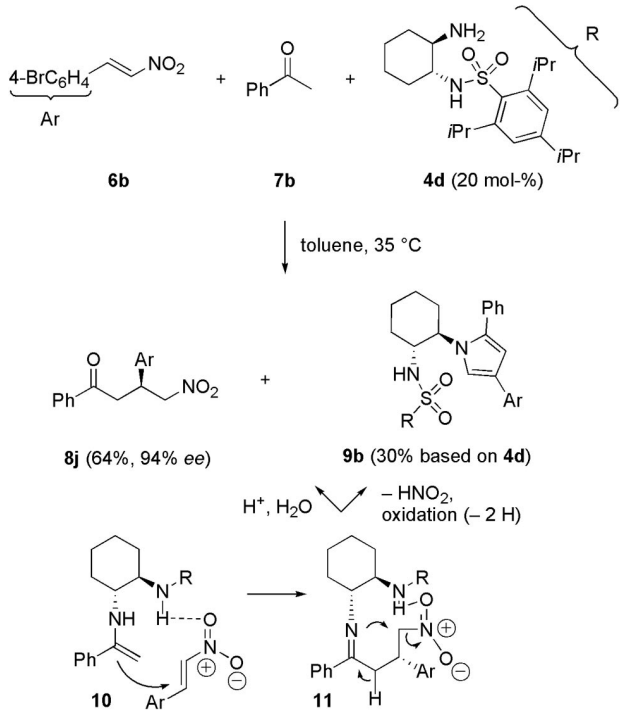
7 **8**

Entry	R^1	Product	Yield [%][a]	*ee* [%][b]
1 (**6a**)[c]	Ph (**7b**)	 **8b**	45	96
2 (**6a**)			72	96
3 (**6a**)[d]			54	87
4 (**6a**)[e]			53	81
5 (**6a**)	4-ClC_6H_4 (**7c**)	 **8c**	70	94
6 (**6a**)	4-BrC_6H_4 (**7d**)	 **8d**	65	94
7 (**6a**)	4-IC_6H_4 (**7e**)	 **8e**	59	98
8 (**6a**)	4-MeC_6H_4 (**7f**)	 **8f**	60	96
9 (**6a**)	4-$MeOC_6H_4$ (**7g**)	 **8g**	51	98
10 (**6a**)	4-$PhOC_6H_4$ (**7h**)	 **8h**	61	97
11 (**6a**)	2-naphthyl (**7i**)	 **8i**	62	98
12 (**6b**)	Ph (**7b**)	 **8j**	64	94
13 (**6c**)	Ph (**7b**)	 **8k**	32	97
14 (**6d**)	Ph (**7b**)		0	–

[a] Isolated yield. [b] Determined by HPLC (Chiralpak AS-H). [c] 20 °C. [d] 50 °C. [e] 70 °C.

The modest turn over cycles and frequencies achieved, which is a general phenomenon with primary amine organocatalysts,[3–7] prompted us to investigate the fate of catalyst

4d in the title reaction. Indeed, we were able to identify the irreversible formation of pyrroles in a three-component reaction between the catalyst, the nitroalkene, and the aromatic ketone as a novel pathway for the catalyst deactivation (Scheme 1).[23] For example, reaction of **6b** and **7b** in the presence of **4d** (20 mol-%) gave rise to **9b** in 30% yield based on the amount of catalyst employed. We propose the formation of intermediate **11** formed by addition of in situ formed enamine **10** to the nitroalkene, which can either undergo hydrolysis to the desired product **8** or can alternatively undergo ring closure with formal elimination of HNO_2 and oxidation to form pyrrole **9**.

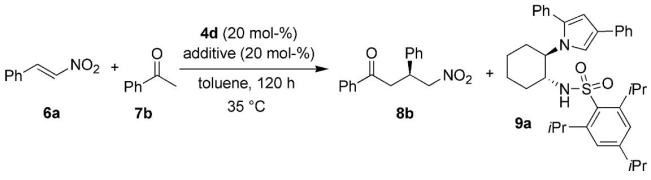


Scheme 1. Catalyst deactivation by irreversible formation of pyrrols.

The mechanistic proposal put forward (Scheme 1) suggests that protic additives should accelerate hydrolysis to yield **8**. On the other hand, protonation could also facilitate the extrusion of nitrous acid as a first step towards the formation of pyrroles **9**. When the various acids, protic solvents, or salts were screened, the pyrrole side products were still observed (Table 4). A notable exception was found with 3,3′,5,5′-tetrabromo-2,2′-biphenol[7] (TBBP), which was able to completely suppress the formation of **9** when equal amounts were employed with respect to **4d**. Nevertheless, the yield of **8** did not improve relative to that obtained for the reaction in which no additives were employed.

Further, following the mechanistic rational depicted in Scheme 1, enamine **10** should be a decisive intermediate in the catalytic cycle. However, only trace amounts of product **8** were observed when the secondary amine **5**, presumably forcing enamine formation, was employed as catalyst, even at elevated temperatures or with benzoic acid as additive.

Table 4. Catalyst deactivation by formation of pyrrole **9a**.



Entry	Additive (mol-%)	Yield **9** [%][a]	Yield **8b** [%]	*ee* [%][b]
1	–	30	72	96
2	PhCOOH	27	58	96
3	AcOH	30	45	95
4	TFA	0	0	–
5	HCOOH	0	0	–
6	PTSA	0	10	92
7	2-ClC_6H_4COOH	30	57	93
8	MeOH	26	64	96
9	NH_4Cl	24	58	95
10	TBBP (20)	0	56	93
11	TBBP (15)	6	53	93
12	TBBP (10)	18	62	93
13	TBBP (5)	20	61	92

[a] Based on **4d**. [b] Determined by HPLC (Chiralpak AS-H).

Conclusions

In conclusion, we have shown that a simple primary amine catalyst can afford excellent enantioselectivity in the conjugate addition of aromatic ketones and nitroalkenes. For the first time, the formation of a pyrrole side product as a mode for catalyst deactivation was observed. Further studies focusing on the development and exploration of diamines as organocatalysts are currently under way.

Experimental Section

Supporting Information (see footnote on the first page of this article): Full experimental procedures and characterization data for compounds **4**, **5**, **8** and **9**.

Acknowledgments

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