Asymmetric Catalysis

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Catalytic Asymmetric [8+2] Cycloaddition: Synthesis of Cycloheptatriene-Fused Pyrrole Derivatives**

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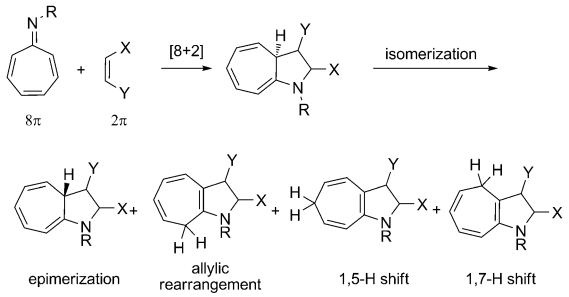
Dedicated to Professor Guo-Qiang Lin on the occasion of his 70th birthday

The higher-order cycloaddition represents a highly valuable strategy for the preparation of medium-sized ring systems.[1] For instance, fulvenes have been applied as 6π components in enantioselective [6+2][2a] and [6+3][2b,c] cycloadditions. For the construction of seven-membered rings,[3–5] asymmetric [5+2][4a,b] and [4+3][5] reactions were developed. However, as a direct method to construct 7,5-fused heterocyclic compounds, the asymmetric [8+2] cycloaddition was less studied.[1d,e] The heteroanalogues of heptafulvenes are the most-studied substrates for the [8+2] cycloadditions.[6–15] In general, the multiple reactivity profiles of the polyene analogues resulted in modest chemical efficiency in such higher-order cycloadditions. For example, tropones have been reported to serve as 4π components in asymmetric [4+2] cycloadditions,[10a] while as 6π components in asymmetric [6+3][11a,b] and [6+4] cycloadditions.[12a] Tropothione received scant concern owing to its inaccessibility and dimerization properties.[14] Comparatively, azaheptafulvene has attracted much attention for it could undergo efficient [8+2] cycloadditions with electron-deficient π systems, as well as for its accessibility and stability (Scheme 1).[15] However, to our knowledge no examples of catalytic asymmetric [8+2] cycloadditions have been reported to date. The cycloheptatriene unit in the initially formed [8+2] adducts could easily undergo isomerization, which led to the occurrence of epimerization (Scheme 1).[16] Moreover, it is too difficult to obtain optically pure bicyclo[5.3.0] ring products by separating these isomers. In the context of ongoing projects in developing asymmetric catalysis promoted by an *N*,*N*′-dioxide–metal complex,[17] we became interested in the enantioselective [8+2] cycloaddition. The azaheptafulvene was chosen as excellent 8π component in the catalytic asymmetric [8+2] cycloaddition,



Scheme 1. The [8+2] cycloaddition of azaheptafulvenes.

affording functionalized cycloheptatriene-fused pyrrole derivatives,[18] which represent a framework found in a number of biologically active molecules.[19]

Initially, we investigated the reaction of azaheptafulvene **1a** with diethyl 2-benzylidenemalonate **2a** promoted by *N*,*N*′-dioxide **L1** with various metals (Table 1, entries 1–4). With $Ni(BF_4)_2{\cdot}6H_2O$ as the central metal salt, the direct [8+2] cycloaddition product **3a** was obtained with the highest *ee* value (75% *ee*). However, the allylic rearrangement product **4a** was detected as the major form, along with the 1,5-and 1,7-H shift products in less than 5% yield (Table 1, entries 1–4). Both the bulky amide subunits and the amino acid backbone of the ligands were crucial for the improvement of the outcome of the reaction. Decrease of the steric hindrance of the amide substituents deteriorated both yields and enantioselectivities (Table 1, entries 4–6). Compared with L-proline-derived ligand **L1** and L-pipecolic acid derived **L4**, L-ramipril-derived *N*,*N*′-dioxide **L5** afforded a higher enantioselectivity (Table 1, entry 8 versus entries 4 and 7). Complete conversion with 93% *ee* was obtained by using catalyst **L5**–Ni-$(BF_4)_2{\cdot}6H_2O$. The ratio of the product **3a** and the allylic rearrangement product **4a** was nearly unchanged even when varying the counteranion of the nickel salts, reaction solvents, temperature, and additives (see the Supporting Information for details); therefore we wondered whether the rearrangement reaction was promoted by the Lewis acid catalyst or other factors. The issue was resolved by column chromatography experiments. When the reaction mixture was purified by chromatography using silica gel (basification by 3% Et_3N), the formation of the allylic rearrangement product **4a** was almost suppressed, albeit a trace of Et_3N was eluted as well (Table 1, entry 9). Accordingly, another ground matrix was chosen as the stationary phase, and the desired product **3a** was obtained in 99% yield and 93% *ee* after being purified by flash chromatography on basic Al_2O_3 (Table 1, entry 10).

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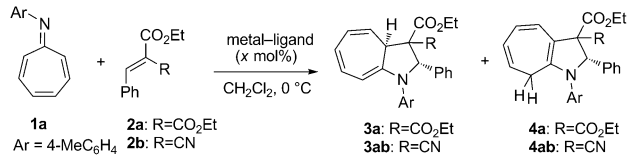
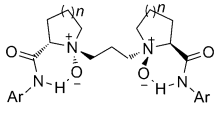
Table 1: Optimization of the reaction conditions.[a]



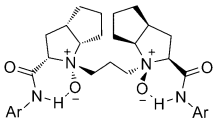
1a Ar = 4-MeC$_6$H$_4$ | **2a**: R=CO$_2$Et **2b**: R=CN | **3a**: R=CO$_2$Et **3ab**: R=CN | **4a**: R=CO$_2$Et **4ab**: R=CN

Entry	Metal	Ligand	*x*	*t* [h]	Yield [%][b]	**3a**/**4a**[c]	*ee* (**3a**) [%][c]
1	Sc(OTf)$_3$	**L1**	10	40	31	22:78	52
2	Mg(ClO$_4$)$_2$	**L1**	10	40	99	25:75	58
3	Co(BF$_4$)$_2$·6H$_2$O	**L1**	10	40	75	21:79	63
4	Ni(BF$_4$)$_2$·6H$_2$O	**L1**	10	40	94	21:79	75
5	Ni(BF$_4$)$_2$·6H$_2$O	**L2**	10	20	88	21:79	35
6	Ni(BF$_4$)$_2$·6H$_2$O	**L3**	10	20	73	19:81	−7
7	Ni(BF$_4$)$_2$·6H$_2$O	**L4**	10	20	92	25:75	39
8	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	10	20	99	26:74	93
9[d]	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	10	20	99	97:3	93
10[e]	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	10	20	99	99:1	93
11[e]	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	0.5	15	99	99:1	93
12[e,f]	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	0.5	2	99	99:1	92
13[e,f]	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	0.1	17	99	99:1	88
14[e,f,g]	Ni(BF$_4$)$_2$·6H$_2$O	**L5**	0.1	2	99	99:1	0
15[f]	–	–	–	24	17	99:1	0
16[f]	–	**L5**	10	24	15	99:1	0

[a] Reaction conditions: metal/**L** (1:1), **1a** (0.11 mmol), and **2a** (0.1 mmol) in CH_2Cl_2 (0.5 mL) at 0°C, and the products were purified by silica gel column chromatography. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase and ^{1}H NMR spectroscopy, and the d.r. > 95:5 was determined by ^{1}H NMR spectroscopy. [d] The product was purified by silica gel (basification by 3% Et_3N) column chromatography. [e] The product was purified by flash chromatography on basic Al_2O_3. [f] At 35°C. [g] **2b** was used to react with **1a** to give **3ab**/**4ab**.



L1: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, *n* = 1
L2: Ar = 2,6-Et$_2$C$_6$H$_3$, *n* = 1
L3: Ar = 2,6-Me$_2$C$_6$H$_3$, *n* = 1
L4: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, *n* = 2

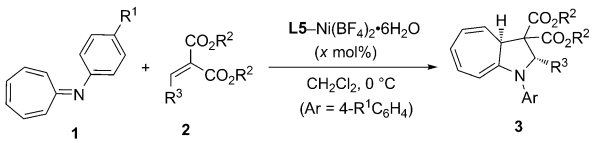


L5: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

Remarkably, the catalytic efficiency was also satisfactory when the catalyst loading was lowered to 0.5 mol% (Table 1, entry 11 versus entry 10). The reaction time could be shortened to 2 h with similar results when the reaction was carried out at 35°C (Table 1, entry 12 versus entry 11). Further lowering the catalyst loading to 0.1 mol% afforded the product in quantitative yield with slightly decreased enantioselectivity (Table 1, entry 13). Meanwhile, when ethyl 2-cyano-3-phenylacrylate **2b** was used as the 2π component, the corresponding racemic adduct was obtained within 2 h (Table 1, entry 14). This result showed that the bidentate dicarbonyl functional groups were indispensable for the chiral control. Besides, blank experiments without metal salt were performed, and lower yields and racemic adducts with high diastereoselectivities (> 95:5 d.r.) were obtained, thereby indicating that the central metal salt was essential for the chiral induction (Table 1, entries 15–16).

This simple catalyst system was quite versatile in the [8+2] cycloaddition with other azaheptafulvenes and alkylidene malonates (Table 2). The 8π components bearing electron-

Table 2: Substrate scope of the asymmetric [8+2] cycloaddition.[a]



1 **2** **3**

Entry	R^1	R^2, R^3	**3**	*x*	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me	Et, Ph	**3a**	0.5	15	99	93
2[d]	MeO	Et, Ph	**3b**	1	24	98	92
3	Cl	Et, Ph	**3c**	0.5	9	99	96
4	Br	Et, Ph	**3d**	0.5	9	95	95
5	Br	Et, Ph	**3d**	0.2	15	95	94
6	Me	Me, Ph	**3e**	0.5	15	99	93
7	Me	Me, 2-FC$_6$H$_4$	**3f**	1	15	99	91
8	Me	Et, 3,4-Cl$_2$C$_6$H$_3$	**3g**	1	11	99	91
9	Me	Et, 4-BrC$_6$H$_4$	**3h**	1	21	93	95
10	Me	Et, 4-CF$_3$C$_6$H$_4$	**3i**	1	15	95	94
11	Me	Et, 3-NO$_2$C$_6$H$_4$	**3j**	1	16	99	92
12	Me	Me, 4-NO$_2$C$_6$H$_4$	**3k**	1	15	99	94
13	Me	Me, 3-MeC$_6$H$_4$	**3l**	1	17	99	95
14	Me	Et, 4-MeC$_6$H$_4$	**3m**	1	15	99	94
15	Me	Et, 4-MeOC$_6$H$_4$	**3n**	0.5	9	99	96
16	Me	Et, 2-thienyl	**3o**	1	16	99	97
17	Me	Et, cyclohexyl	**3p**	1	8	90	95
18[d,e]	Me	Et, Et	**3q**	2	35	38	93
19[d,f]	Me	Et, *i*Pr	**3r**	2	22	92	96

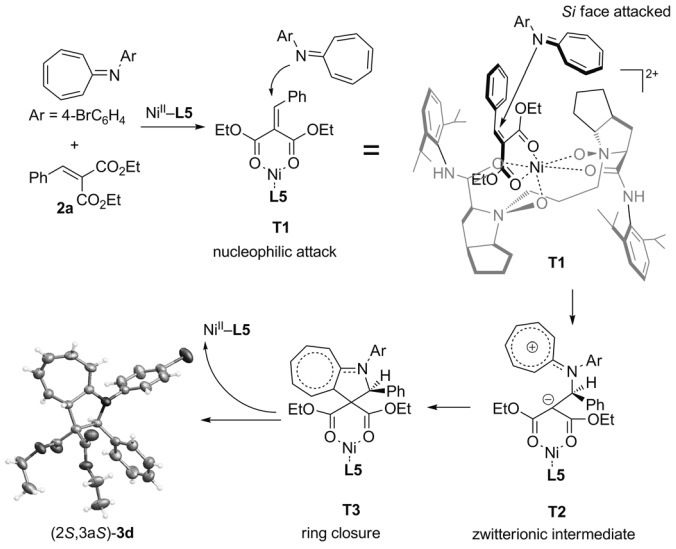
[a] Reaction conditions: Ni(BF$_4$)$_2$·6H$_2$O/**L5** (1:1), **1** (0.11 mmol), and **2** (0.1 mmol) in CH_2Cl_2 (0.5 mL) at 0°C, and the products were purified by flash chromatography on basic Al_2O_3. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase, and the d.r. > 95:5 was determined by ^{1}H NMR spectroscopy. The total amount of isomerization products was less than 5%. [d] The azaheptafulvene was generated in situ from the tetrafluoroborate salt with Et_3N. [e] **3q**/**4q** = 3:7. [f] **3r**/**4r** = 23:76. **4** is the corresponding allylic rearrangement product (see Scheme 1).

donating or electron-withdrawing substituents on the *N*-aryl group underwent efficient cyclization in excellent enantioselectivities (92–96% *ee*), high diastereoselectivities (> 95:5 d.r.), and high yields (Table 2, entries 1–5). Dimethyl 2-benzylidenemalonate gave comparable enantioselectivity and yield (Table 2, entry 6). The reactions were remarkably tolerant of functional groups regardless of the electronic properties and steric hindrance of the substituents on the 2π components (Table 2, entries 7–15). Among the substrates **2** investigated, *o*-fluoro-substituted and disubstituted ones afforded slightly lower enantioselectivities (Table 2, entries 7, 8 versus entries 9–15). Additionally, olefins containing heteroaromatic and aliphatic groups also underwent the [8+2] cycloaddition, affording the desired adducts with high enantioselectivities (93–97% *ee*; Table 2, entries 16–19). Allylic rearrangement products could not be excluded for substrates **2q** and **2r** derived from aliphatic aldehydes (Table 2, entries 18–19). In all cases, the cyclization reactions exhibited excellent diastereoselectivity, and only *trans*-isomers of **3** were found. The absolute configuration of the cycloheptatriene-fused pyrrole derivative **3d** was determined to be (2*S*, 3a*S*) by single-crystal X-ray diffraction analysis.[20]

To further evaluate the synthetic potential of the catalytic system, a gram-scale synthesis of chiral cycloheptatriene-

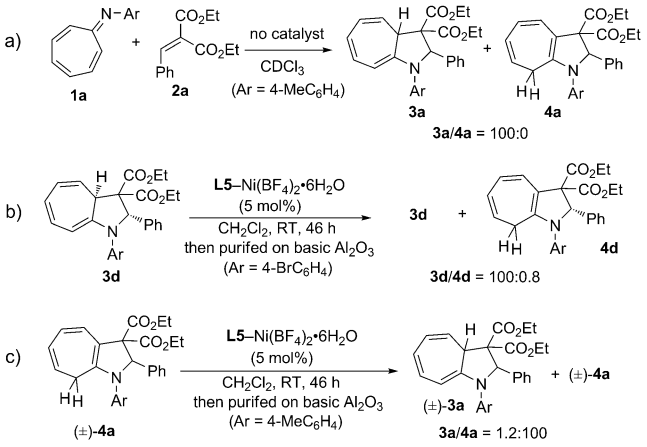
fused pyrrole **3a** was carried out. By treatment of the starting material (2.5 mmol) in the presence of *N*,*N*′-dioxide **L5**–Ni^{II} complex (0.5 mol%) at 35°C for 4 h, the corresponding adduct **3a** (1.10 g) was obtained without loss of the reactivity, diastereoselectivity, and enantioselectivity (see the Supporting Information for details).

To understand the [8+2] cycloaddition process, a possible stepwise pathway was assumed based on previous reports (Scheme 2).[14d,16b–d] In the initial step, the tetradentate *N*,*N*′-dioxide **L5** and the bidentate alkylidene malonate **2a** coordinated with Ni^{II} to form an octahedral geometry as the intermediate **T1**. The *Re* face of the alkylidene malonate was shielded by the neighboring 2,6-diisopropylphenyl group of the ligand, and the azaheptafulvene predominantly attacked from the *Si* face. Thus the zwitterionic intermediate **T2** was generated with the positive charge of the 8π component delocalized within the ring. Then immediately ring closure occurred (**T3**) to yield adduct **3d** and release the catalyst.



Scheme 2. Proposed reaction pathway for the catalytic asymmetric [8+2] cycloaddition. In the ORTEP representation of **3d**, thermal ellipsoids are set at 30% probability.

The structure of the allylic rearrangement product (±)-**4h** was determined by analyzing the single-crystal structure.[20] In the reaction of **1a** and **2a** in $CDCl_3$ without any catalyst, only [8+2] cycloadduct **3a** was detected by ^1H NMR spectroscopy, and no **4a** was observed even one week later (Scheme 3a). This phenomenon and the column chromatography experiments (Table 1, entries 8–10) indicated that the allylic rearrangement[21] happened during the purification process. Acidic silica gel promoted the allylic rearrangement reaction, while basic Al_2O_3 did not promote the process. When optically pure [8+2] adducts **3d** or (±)-**4a** were stirred independently with the Ni^{II}–**L5** catalyst for 46 h, no transformation between the two isomers was found (Scheme 3b,c). This result implied that this chiral Lewis acid catalyst is efficient for the exclusive formation of the desired product.



Scheme 3. Investigation of the transformation between the [8+2] cycloadduct and the related allylic rearrangement product.

In summary, we have developed the first catalytic asymmetric [8+2] cycloaddition reaction of azaheptafulvenes with alkylidene malonates. Remarkably, with the chiral *N*,*N*′-dioxide **L5**–Ni^{II} complex (0.2–2 mol%), the reaction worked well, affording the desired cycloheptatriene-fused pyrrole derivatives in excellent diastereoselectivities (>95:5 d.r.), and enantioselectivities (91–97% *ee*). Furthermore, the allylic rearrangement reaction was proved to be promoted by silica gel, which could be almost avoided by flash chromatography on basic Al_2O_3.

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[20] CCDC 892341 (**3d**) and 892839 ((±)-**4h**) contain 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.

[21] The mechanism of the allylic rearrangement reaction was still unknown, for more information, see the Supporting Information.

