Asymmetric Cycloaddition

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Rhodium(II)-Catalyzed Enantioselective Synthesis of Troponoids**

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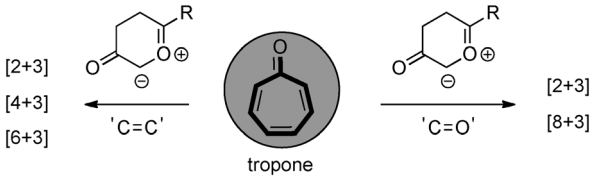
Abstract: *We report a rhodium(II)-catalyzed highly enantioselective 1,3-dipolar cycloaddition reaction between the carbonyl moiety of tropone and carbonyl ylides to afford troponoids in good to high yields with excellent enantioselectivity. We demonstrate that α-diazoketone-derived carbonyl ylides, in contrast to carbonyl ylides derived from diazodiketoesters, undergo [6+3] cycloaddition reactions with tropone to yield the corresponding bridged heterocycles with excellent stereoselectivity.*

Biology-oriented synthesis (BIOS) serves as a guiding principle for the design and synthesis of focused compound collections with diverse bioactivity.[1] In particular, natural products (NPs) provide inspiration for BIOS, since they represent the area of chemical space explored by nature, and hence can be regarded as "privileged" starting points for the syntheses. NPs are frequently complex and rich in stereogenic centers. Therefore, the development of efficient enantioselective methods is highly desirable.[2] The tropone scaffold defines the structural core of the troponoids, which comprise numerous natural products with diverse bioactivity.[3] Tropones are highly valuable and readily available seven-membered-ring-containing compounds that can undergo cycloaddition reactions to afford annulated products of high medicinal importance.[4] However, catalytic enantioselective cycloaddition reactions of tropones are rare.[5]

Dirhodium(II)-complex-catalyzed 1,3-dipolar cycloaddition reactions of diazocarbonyl compounds are powerful transformations for the construction of complex oxapolycyclic systems,[6–8] and catalytic enantioselective reactions employing chiral Rh^{II} carboxylates have been developed.[9,10] In contrast to non-asymmetric transformations,[11–13] enantioselective 1,3-dipolar cycloaddition reactions of carbonyl ylides with heterodipolarophiles have rarely been explored.[14] There are only three reported cases of the catalytic enantioselective 1,3-dipolar cycloaddition of carbonyl ylides with aldehydes as the dipolarophile,[14] and the corresponding cycloaddition with ketones is unprecedented. The enantioselective cycloaddition of tropone with carbonyl ylides has not yet been explored. These facts inspired us to investigate the reactivity of tropone in rhodium(II)-catalyzed tandem carbonyl-ylide-formation/1,3-dipolar-cycloaddition reactions, which should rapidly generate molecular complexity and provide efficient access to structurally diverse troponoid scaffolds (Scheme 1).



Scheme 1. Plausible cycloaddition reactions of tropone and a carbonyl ylide.

Herein, we report a catalytic enantioselective intermolecular cycloaddition reaction between carbonyl ylides derived from diazodiketoesters **2** and tropone (**1**) as the dipolarophile to provide a diverse range of 5-alkoxylactone derivatives **3** (Table 2). We also demonstrate that carbonyl ylides derived from α-diazoketones undergo higher-order cycloaddition reactions, which is remarkable, since enantioselective transformations involving tropone as a 6π dipolarophile are rare.[5b–e] The chemoselective reaction of carbonyl ylides with the conjugated 6π system of tropone, instead of the carbonyl functionality, provides efficient and facile access to bridge-containing tricyclic heterocycles embodying four stereogenic centers (Table 3). The observed substrate-controlled chemoselective switch in reactivity provides a highly interesting example of programmable synthesis.[15,2e]

We began our studies by treating tropone (**1**) with diazodiketoester **2a** (1.5 equiv) in the presence of various rhodium(II) carboxylates (1 mol%) in $PhCF_3$ as the solvent at room temperature (Table 1, entries 1–6). The reaction pro-

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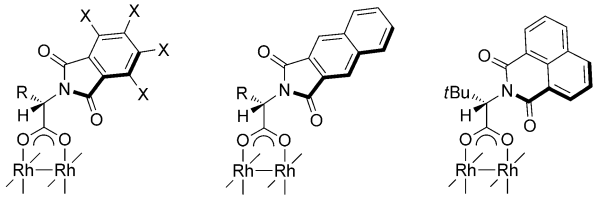
Table 1: Screening of reaction conditions for the synthesis of **3a**.[a]

Entry	Catalyst (mol%)	*t* [h]	Yield [%]	*ee* [%]
1	**C1** (1)	3	74	62
2	**C2** (1)	3	34	13
3	**C6** (1)	3	89	77
4	**C5** (1)	3	71	67
5	**C3** (1)	3	74	99
6	**C4** (1)	3	58	50
7[b]	**C3** (1)	12	trace	n.d.
8	**C3** (0.25)	15	74	98
9[c]	**C3** (0.05)	24	26	98

[a] Reaction conditions: **1** (0.1 mmol), **2a** (1.5 equiv), catalyst, solvent: $PhCF_3$ (0.1 M), room temperature. [b] The reaction was carried out at 0 °C. [c] The reaction did not proceed to completion. n.d. = not determined. **C1**: $[Rh_2\{(S)\text{-pttl}\}_4]$; **C2**: $[Rh_2\{(S)\text{-ptil}\}_4]$; **C3**: $[Rh_2\{(S)\text{-tcpttl}\}_4]$; **C4**: $[Rh_2\{(S)\text{-tfpttl}\}_4]$; **C5**: $[Rh_2\{(S)\text{-bpttl}\}_4]$; **C6**: $[Rh_2\{(S)\text{-nttl}\}_4]$.

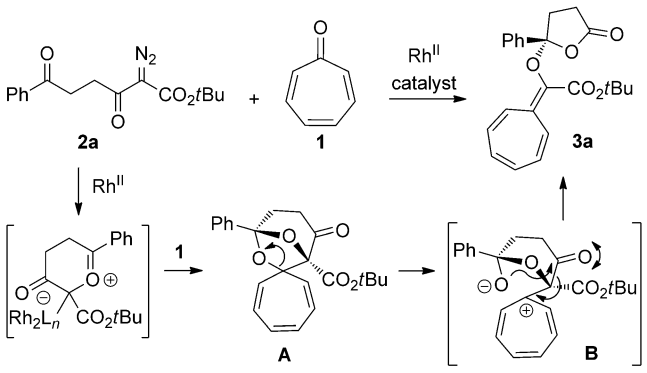


C1: R = *t*Bu, X = H
C2: R = *s*Bu, X = H
C3: R = *t*Bu, X = Cl
C4: R = *t*Bu, X = F

C5: R = *t*Bu

C6

ceeded smoothly in the presence of catalyst **C1** to give cycloadduct **3a** as the sole product, instead of the expected spirocyclic compound **A** (Scheme 2). The formation of **3a** proceeds via intermediate **A** through a cascade reaction. We propose the formation of **A** by the [3 + 2] cycloaddition of



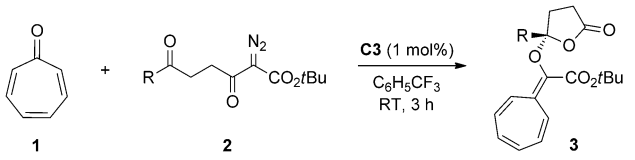
Scheme 2. Proposed pathway for the formation of product **3a**.

a carbonyl ylide with the keto group of tropone. Subsequently, under the reaction conditions, intermediate **A** is converted into zwitterion **B**, which then undergoes cyclization and rearrangement to generate lactone **3a**.

Product **3a** was obtained in 74% yield and with 62% *ee* (Table 1, entry 1). The yield and enantioselectivity dropped drastically upon the replacement of **C1** with the isoleucine-derived catalyst **C2** (Table 1, entry 2). Although the benzene-fused phthaloyl catalyst **C5** did not increase the enantioselectivity of the formation of **3a** substantially (67% *ee*; Table 1, entry 4), an improvement in yield and enantioselectivity was observed with the 1,8-naphthalimide-*tert*-leucine derived catalyst **C6** (77% *ee*; entry 3). Gratifyingly, the tetrachlorophthalimide-derived catalyst **C3** developed by Hashimoto and co-workers[10] delivered the cycloadduct **3a** in 74% yield and with 99% *ee* (Table 1, entry 5). Interestingly, a sharp decline in enantioselectivity was observed upon the replacement of **C3** with the corresponding fluoro-containing catalyst **C4** (Table 1, entry 6). Subsequently, we screened a variety of solvents and investigated the use of different catalyst loadings. However, none of the solvents tested gave better results than $PhCF_3$ (see the Supporting Information). At a lower temperature, the reaction did not proceed (Table 1, entry 7). High enantioselectivity was retained even with catalyst loadings as low as 0.05 mol%, but yields were lower and longer reaction times were required (see the Supporting Information). The absolute configuration of cycloadduct **3a** was established by vibrational circular dichroism (VCD) spectroscopy, and the configuration of the other cycloadducts was assigned by analogy (see the Supporting Information).

Having optimized the reaction conditions, we explored the scope of the transformation by treating tropone (**1**) with a set of electronically and structurally diverse diazodiketoester derivatives **2** (Table 2). The reaction was very versatile, and various substitution patterns on the phenyl ring of diazodiketoester **2** were tolerated. The 4-methyl- and 4-hexyl-substituted phenyl diazo derivatives **2b** and **2c** underwent smooth transformation in a completely chemoselective manner to furnish the desired cycloadducts **3b** and **3c** in good yield with excellent enantioselectivity (Table 2, entries 1

Table 2: Scope of the reaction.[a]



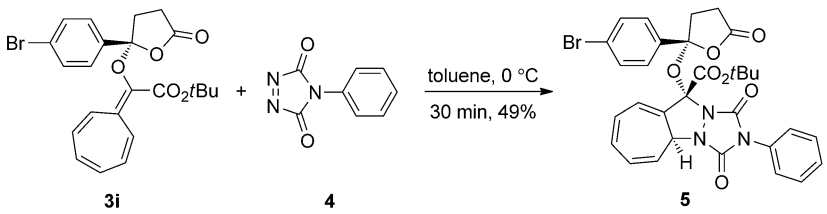
1 **2** **3**

Entry	Product	R	Yield [%][b]	*ee* [%][c]
1	**3b**	4-MeC_6H_4	71	97
2	**3c**	4-*n*HexC_6H_4	86	99
3[d]	**3d**	4-*i*PrC_6H_4	66	99
4[d]	**3e**	4-*t*BuC_6H_4	69	99
5[d,e]	**3f**	4-$MeOC_6H_4$	73	98
6	**3g**	4-FC_6H_4	80	99
7	**3h**	4-ClC_6H_4	77	94
8	**3i**	4-BrC_6H_4	78	98
9[d,e]	**3j**	2,5-$Me_2C_6H_3$	73	98
10[d,e]	**3k**	3-F-4-$MeOC_6H_3$	79	99
11	**3l**	Me	85	76
12	**3m**	*i*Pr	95	77

[a] Reaction conditions: **1** (0.1 mmol), **2** (1.5 equiv), **C3** (1 mol%), solvent: $PhCF_3$ (0.1 M). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] The reaction was carried out with 2 mol% of **C3**. [e] The reaction was carried out with 2 equivalents of derivative **2**.

and 2). Furthermore, a high level of asymmetric induction was maintained in the case of derivatives **2d** and **2e**, with sterically encumbered substituents (Table 2, entries 3 and 4). Pleasingly, aryl diazo derivatives **2** containing both electron-donating and electron-withdrawing substituents reacted efficiently with tropone to deliver the expected products **3f–i** in high yield and with excellent enantioselectivity (94–99% *ee*; Table 2, entries 5–8). Importantly, the reaction was tolerant of *ortho* substitution in the dimethyl-substituted derivative **2j**, and the corresponding product **3j** was obtained in 73% yield with 98% *ee* (Table 2, entry 9). The efficacy of the reaction remained unaltered in the case of 3-fluoro-4-methoxy derivative **2k**, from which the product **3k** was synthesized with excellent stereoselectivity (Table 2, entry 10). The reaction was found to be compatible with aliphatic diazodiketoester-derived carbonyl ylides, and moderate enantioselectivity (76% *ee*) was observed in the reaction of methyl-substituted derivative **2l** (Table 2, entry 11). Upon replacement of the methyl substituent with a sterically more bulky isopropyl substituent, a higher yield and a similar level of enantioselectivity were observed in the formation of **3m** (Table 2, entry 12).

To further functionalize the products, we decided to exploit the reactivity of the conjugated 8π system embedded in products **3**. Accordingly, a diastereoselective [8+2] cycloaddition of product **3i** and *N*-phenyltriazolinedione (**4**) yielded the fused-ring compound **5**, with one tertiary and two quaternary stereogenic centers (Scheme 3). The solid-state molecular structure of **5** was determined by single-crystal X-ray diffractional analysis, which unambiguously revealed the absolute configuration of product **5** and reaffirmed the absolute configuration of compounds **3**.

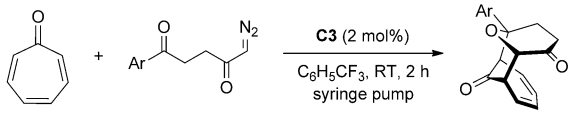


3i 4 5

Scheme 3. Diastereoselective [8+2] cycloaddition of product **3i** and *N*-phenyltriazolinedione (**4**).

We then explored the use of carbonyl ylides derived from α-diazoketones as dipoles in this transformation. This possibility is intriguing owing to the reactivity difference arising from the different HOMO/LUMO energy levels of carbonyl ylides derived from diazodiketoesters and α-diazoketones.[11a] Upon the treatment of the carbonyl ylide derived from α-diazoketone **6a** with tropone **1** in the presence of catalyst **C3**, the bridged polyheterocyclic compound **7a** was obtained as a single diastereoisomer (>20:1) with high enantioselectivity (94% *ee*; Table 3, entry 1). In this case, the carbonyl ylide underwent [6+3] cycloaddition with the conjugated triene system of tropone. We found that the best yield was obtained when the corresponding diazo compound was added over 1 h by the use of a syringe pump. To explore the scope of the

Table 3: Scope of the reaction.[a]



1 6 7

Entry	Product	Ar	Yield [%][b]	*ee* [%][c]
1	**7a**	C_6H_5	78	94
2	**7b**	4-*n*HexC_6H_4	55	92
3	**7c**	4-*i*PrC_6H_4	56	89
4	**7d**	4-FC_6H_4	30	92
5	**7e**	4-BrC_6H_4	66	87
6	**7f**	4-MeOC_6H_4	–	–

[a] Reaction conditions: **1** (0.1 mmol), **6** (2.0 equiv), **C3** (2 mol%), solvent: $C_6H_5CF_3$ (0.1 M). All products were obtained with d.r. >20:1. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC on a chiral stationary phase.

reaction, we exposed tropone to a diverse set of α-diazoketones **6** (2.0 equiv) in the presence of **C3** (2 mol%) at room temperature. Pleasingly, electronically diverse aryl diazo carbonyl substrates with electron-rich and electron-withdrawing substituents on the phenyl ring underwent efficient transformation to yield the corresponding cycloadducts **7b–e** in moderate to good yield and with excellent diastereo- (>20:1) and enantioselectivity (Table 3, entries 2–5). Unfortunately, we did not observe the formation of the desired product when the electron-rich 4-methoxy-substituted derivative **6f** was used as the dipole precursor, possibly as a result of competing C–H insertion of the rhodium(II) carbenoid into the activated aromatic ring. It is known that the C–H insertion of rhodium carbenoids can be a competitive process with carbonyl-ylide formation and cycloaddition.[11a] The absolute configuration of cycloadduct **7a** was established by VCD spectroscopy, and the configuration of the other cycloadducts was assigned by analogy (see the Supporting Information).

In summary, we have developed a 1,3-dipolar cycloaddition reaction of carbonyl ylides derived from diazodiketoesters with tropone under the catalysis of dirhodium tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate] ($[Rh_2\{(S)\text{-tcpttl}\}_4]$, **C3**) that affords the corresponding cycloadducts in good to high yields and with excellent enantioselectivity. We also demonstrated that carbonyl ylides derived from α-diazoketones undergo facile [6+3] cycloaddition reactions with tropone to furnish the corresponding bridged tricyclic compounds in moderate to good yields and with excellent stereoselectivity. The substrate-controlled switch in reactivity of tropone provides an opportunity for the catalytic enantioselective programmable synthesis of complex products.

Keywords: asymmetric catalysis · carbonyl ylides · cycloaddition · rhodium · tropone

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[15] *p*-Quinone systems had earlier been reported to undergo rhodium(II)-catalyzed dipolar cycloaddition with carbonyl ylides to give both C=C and C=O addition products. The product ratio was shown to be dependent on the solvent and catalyst used.[12b]

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Communications

Asymmetric Cycloaddition

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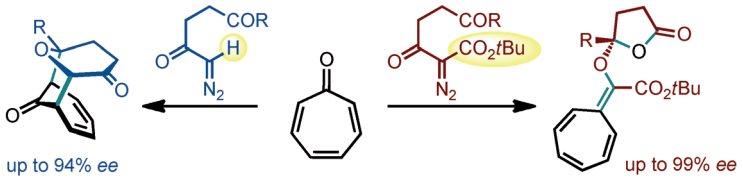
Rhodium(II)-Catalyzed Enantioselective Synthesis of Troponoids



Decisive dipoles: In the rhodium(II)-catalyzed asymmetric 1,3-dipolar cycloaddition of tropone with carbonyl ylides, a programmable chemoselective reaction with the keto group or the 6π system of tropone was controlled by the substrate (see scheme). The developed method enables the synthesis of complex products in highly enantiomerically enriched form.