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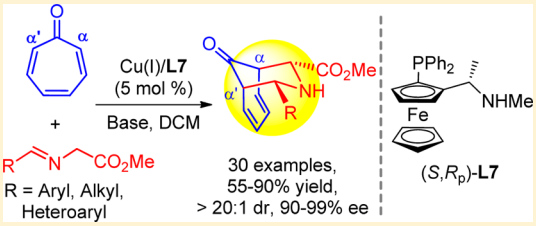
Cu(I)-Catalyzed Regio- and Stereoselective [6 + 3] Cycloaddition of Azomethine Ylides with Tropone: An Efficient Asymmetric Access to Bridged Azabicyclo[4.3.1]decadienes

Huai-Long Teng,[†] Lu Yao,[†] and Chun-Jiang Wang*[,†,‡]

[†]College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, China 430072
[‡]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, China, 300071

Supporting Information

ABSTRACT: An unprecedented Cu(I)-catalyzed asymmetric [6 + 3] cycloaddition of tropone with azomethine ylides was reported, which performs well over a broad scope of substrates and offers a unique and facile access to the synthetically useful bridged azabicyclo[4.3.1]decadiene derivatives in good yields with high levels of diastereoselectivities and enantioselectivities under mild conditions.

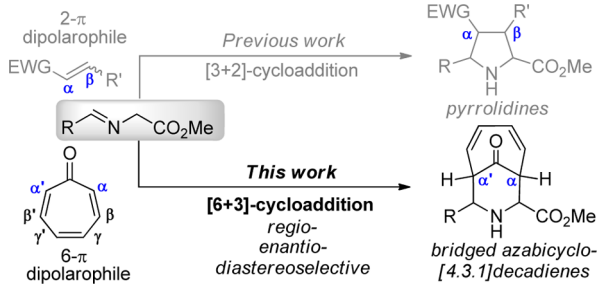


INTRODUCTION

Transition-metal-catalyzed cycloaddition reactions are one of the commonly used methods for the construction of bridge-containing carbocyclic and heterocyclic structures, which exist in numerous natural products and active pharmaceutical ingredients.[1] Tropone and the related compounds in troponoid family have been recognized as valuable synthons of natural products[2] and suitable partners in higher order cycloadditions[3] since the identification of tropolone moiety as a key unit of alkaloids.[4] Many impressive syntheses of bridge-containing carbocycles employing tropones as the C_n synthons have been reported. For example, a phosphoramidite-Pd complex catalyzed efficient asymmetric [6 + 3] cycloaddition of tropone with trimethylenemethane has been reported by Trost;[5] Yamamoto and co-workers reported an efficient Al-catalyzed asymmetric inverse-electron-demand [4 + 2] Diels–Alder reaction of tropones.[6] Lu's seminal studies showed PPh_3-catalyzed [6 + 3] cycloaddition of tropone with allylic compounds.[7,8] One common feature of these tropone-involving cycloadditions is that the other partner is an all-carbon (C2∼C4) reactant. Readily available imino esters are commonly used as heteroatom-containing dipoles in [3 + 2] cycloadditions with electron-deficient olefins (2-π dipolarophile) for the construction of five-membered heterocyclic pyrrolidines.[9,10] The cycloaddition of imino esters with tropone could provide an attractive approach toward optically active molecules possessing an azabicyclic motif (Scheme 1).

In conjunction with our continuing efforts in imino ester chemistry,[11] we envision that *in situ*-generated azomethine ylides from imino esters could be employed as the hetero three-atom synthons in the cycloaddition with tropone (6-π dipolarophile). Herein we report the asymmetric [6 + 3] cycloaddition of tropone with azomethine ylides catalyzed by a Cu(I)/(S,R_P)-ferrocenyl-based chiral ligand, providing an efficient and facile access to optically active azabicyclo[4.3.1]-decadiene derivatives with high diastereoselectivity and excellent enantioselectivity.

Scheme 1. Azomethine Ylides As Hetero Three-Atom Synthons in [3 + 2] Cycloaddition (Previous Work) and [6 + 3] Cycloaddition (This Work)



RESULTS AND DISCUSSION

Initial Test to Probe the Possible Reaction Pathway. Initially, we chose commercially available tropone **1** and *N*-(4-chlorobenzylidene)glycine methyl ester **2a** as the model substrates in the presence of 5 mol % of $Cu(CH_3CN)_4BF_4$/PPh_3 complex as the catalyst and 15 mol % of Et_3N as the base in CH_2Cl_2 at room temperature. The reaction finished in <5 h and delivered the azabicyclo[4.3.1]decadiene **3a** as a single isomer via [6 + 3] pathway with excellent regioselectivity and high diastereoselectivity (>20:1) (Scheme 2). No reaction occurred in the absence of the Cu(I)/PPh_3 complex. Compared with Ag(I)-complex derived from AgOAc or AgOTf, the Cu(I)-complex afforded better catalytic activity, leading to a faster reaction rate and a better yield (see Supporting Information for

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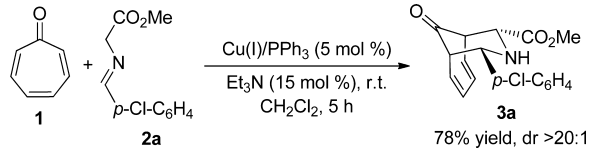
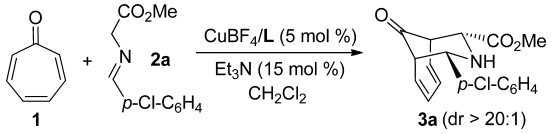
Scheme 2. Initial Discovery of Cu(I)/PPh_3-Catalyzed [6 + 3] Cycloaddition of Tropone 1 with Azomethine Ylide 2a



the details). Either a [3 + 2] or a [8 + 3] adduct was not observed.[12] The cycloadduct **3a** is stable and no further reaction occurred.

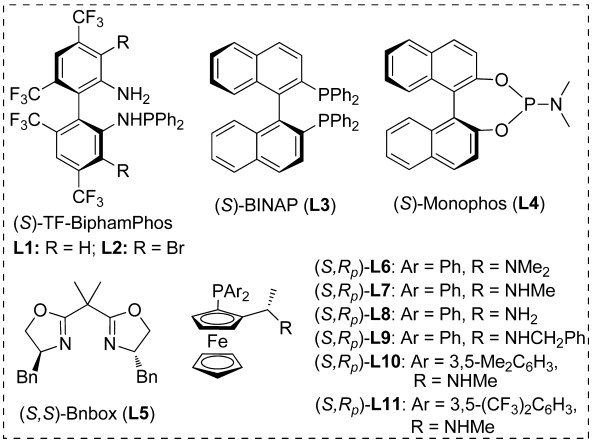
Catalytic Asymmetric [6 + 3] Cycloaddition of Azomethine Ylides with Tropone. Encouraged by these results, we then began to develop an asymmetric variant of this [6 + 3] annulation. A wide variety of chiral ligands was investigated, and the representative results were summarized in Table 1. TF-BiphamPhos,[11] exhibiting excellent catalytic selectivity in the asymmetric reactions of azomethine ylides, was first tested in this [6 + 3] cycloaddition reaction. Combined with **L1** and **L2**, $CuBF_4$ showed high catalytic activity and provided the desired adduct exclusively in good yields with excellent diastereoselectivity albeit with low enantioselectivity. Then, other commercially available chiral ligands were tested: bisphosphine ligand (*S*)-BINAP(**L3**)[13] showed pretty low catalytic activity and enantioselectivity, while 35% ee and 10% ee were achieved when (*S*)-Monophos(**L4**)[14] and bidentate (*S,S*)-Bn-Box(**L5**)[15] were used as the chiral ligand, respectively (Table 1, entries 3−5). Considering the significant role of ferrocenyl-phosphine ligands playing in the [3 + 2] cycloaddition of azomethine ylides,[16] we further screened chiral ferrocenyl-based P,N-ligands.[17] Ligand **L7** exhibited the best performances affording the desired cycloadduct **3a** in good yield with excellent stereoselectivity (>20:1 dr, 82% ee) (entry 7). It is noteworthy that asymmetric induction of N-disubstituted and monosubstituted ligands **L6**, **L7**, and **L9** was found to be superior to that of N-unsubstituted chiral ligand **L8** (entries 6, 7, and 10). Catalytic activity decreased significantly when the phenyl group on the phosphorus atom of the ligand **L7** was replaced by the bulky and electron-donating xylyl group or electron-withdrawing 3,5-bis(trifluoromethyl)-phenyl group (entries 11 and 12). The catalyst prepared from Cu(I):**L7** in 1:1 or 1:2 ratio showed the very similar results (entries 7 and 8). After further optimization of the reaction temperature and reaction time with **L7**, cycloadduct **3a** was isolated in 76% yield, > 20:1 dr, and 97% ee after 24 h at −10 °C (entry 14).

Table 1. Optimization for the Catalytic Asymmetric [6 + 3] Cycloaddition of Tropone 1 with Azomethine Ylide 2a[a]



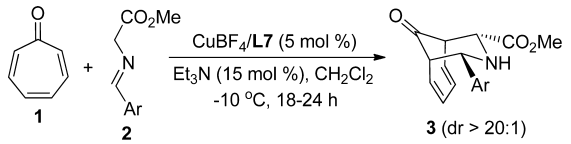
entry	L	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**L1**	rt	24	60	25
2	**L2**	rt	24	50	30
3	**L3**	rt	24	16	8
4	**L4**	rt	24	45	35
5	**L5**	rt	12	50	10
6	**L6**	rt	3	56	74
7	**L7**	rt	3	72	82
8[d]	**L7**	rt	3	74	82
9	**L8**	rt	3	56	27
10	**L9**	rt	3	32	77
11	**L10**	rt	24	38	87
12	**L11**	rt	24	29	79
13	**L7**	0	18	65	92
14	**L7**	−10	24	76	97

[a]All reactions were carried out with 0.24 mmol of **2a** and 0.20 mmol of **1** in 1 mL of CH_2Cl_2. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b]Isolated yield. [c]dr was determined by crude ^1H NMR, and ee was determined by HPLC analysis. [d]$CuBF_4$ is 5 mol %, and **L7** is 11 mol %.



Under the optimized reaction conditions, the substrate scope of this [6 + 3] cycloaddition was investigated, and the results are listed in Table 2. To our delight, we found that a wide array

Table 2. Substrate Scope of the Catalytic Asymmetric [6 + 3] Cycloaddition of Tropone 1 with Aryl Azomethine Ylides 2[a]



entry	Ar	prod.	yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4 (**2a**)	**3a**	76	97
2	*m*−Cl-C_6H_4 (**2b**)	**3b**	83	93
3	*p*-Br-C_6H_4 (**2c**)	**3c**	80	97
4	*p*-CF_3-C_6H_4 (**2d**)	**3d**	85	96
5	*p*-F-C_6H_4 (**2e**)	**3e**	90	98
6	*p*-NO_2−C_6H_4 (**2f**)	**3f**	82	91
7	*p*-CN-C_6H_4 (**2g**)	**3g**	68	96
8	*p*-CO_2Me-C_6H_4 (**2h**)	**3h**	83	95
9	Ph (**2i**)	**3i**	75	96
10	*p*-OMe-C_6H_4 (**2j**)	**3j**	72	94
11	*m*-OMe-C_6H_4 (**2k**)	**3k**	70	95
12[d]	*o*-OMe-C_6H_4 (**2l**)	**3l**	62	95
13	*p*-Me-C_6H_4 (**2m**)	**3m**	78	95
14	*m*-Me-C_6H_4 (**2n**)	**3n**	65	93
15[d]	*o*-Me-C_6H_4 (**2o**)	**3o**	72	95
16	*p*-^{t}Bu-C_6H_4 (**2p**)	**3p**	78	99
17[e]	2-naphthyl (**2q**)	**3q**	82	90
18[e]	2-Thienyl (**2r**)	**3r**	71	90

[a]All reactions were carried out with 0.24 mmol of **2** and 0.20 mmol of **1** in 1 mL of CH_2Cl_2. [b]Isolated yield. [c]dr was determined by the crude ^1H NMR, and ee was determined by HPLC analysis. [d]Carried out at −10 °C for 30 h. [e]Carried out at −20 °C for 48 h.

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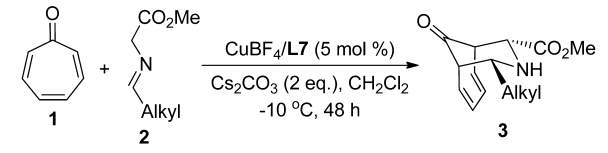
of azomethine ylide precursors **2a**−**2p** derived from aryl aldehydes bearing electron-deficient (Table 2, entries 1−8), electron-neutral (entry 9), and electron-rich substituents (entries 10−16) on the aryl rings were readily applicable in this reaction, providing the corresponding cycloadducts in good yields (62−90%), exclusive regioselectivity, excellent diastereoselectivities (>20:1 dr), and high enantioselectivities (91−99% ee). The catalyst system also tolerated changes in the substitution pattern of the aromatic ring. It is noteworthy that high diastereoselectivity and excellent enantioselectivity could be achieved with sterically hindered *ortho*-methoxyl **2l** and *ortho*-methyl substituted imino esters **2o**, although longer reaction time was required (entries 12 and 15). Additionally, heteroaromatic 2-thienylaldehyde derived imino ester **2r** was also viable azomethine ylide precursor as 2-naphthylaldehyde derived imino ester **2q**, delivering the corresponding cycloadduct **3r** in 71% yield with >20:1 dr and 90% ee (entry 18).

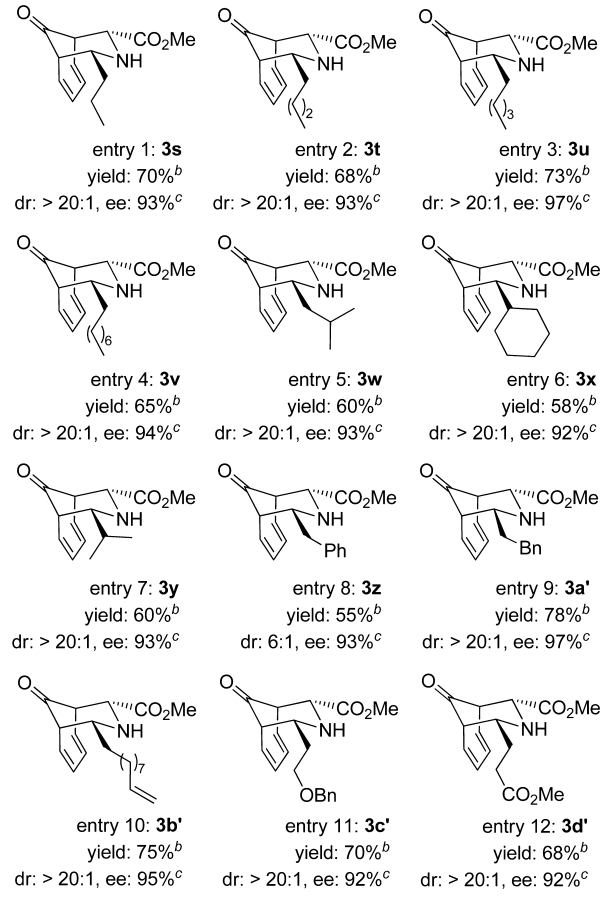
Encouraged by the excellent results with imino esters derived from aryl aldehydes, we then investigated the [6 + 3] cycloaddition with the aliphatic aldehyde-derived imino esters. Due to the lower reactivity of the aliphatic imino esters,[9] strong inorganic base Cs_2CO_3 was used instead of Et_3N. As shown in Table 3, the length of the linear alkyl group in the imino moiety had little effect on the stereoselectivity of this tropone-involved annulation, and substrates with primary *n*-alkyl substituent such as *n*-propyl, *n*-butyl, and *n*-octyl groups all have afforded high diastereoselectivity and excellent enantioselectivity (Table 3, entries 1−4). Both benzyl and homobenzyl groups were well tolerated, giving rise to the cycloadducts in good yield with excellent enantioselectivity (entries 8 and 9). To further probe the impact of varying the alky substituent on this reaction, several substrates with branched and sterically bulky alkyl substituents such as *iso*-butyl, *iso*-propyl, and cyclohexyl were employed, and the cycloaddition proceeded smoothly to form the desired adducts with similarly high levels of regio- and diastereo-/enantioselectivity (entries 5−7). Imino esters derived from aliphatic aldehyde bearing C=C bond, ether, and ester moiety were also viable substrates providing the desired cycloadducts in good yield with high stereoselectivity (entries 10−12). In most cases, nearly one isomer was observed with the exception of benzyl substituted cycloadduct **3z** (entry 8). The limitation is that ester-substituted tropones were not tolerated in this system delivering unidentified mixtures probably due to the lability of those compounds under basic reaction conditions.[18] The relative and absolute configuration of the cycloadduct **3a** was determined to be (1*S*,6*R*,7*R*,9*S*) by X-ray analysis[19] (Figure 1).

Linear Effect and Proposed Reaction Mechanism. In order to obtain some mechanistic information on the coordination environment around the metal center and the possible active species, we investigated the relationship between the ee values of the chiral ligand and the corresponding ee values of the cycloadduct in this transformation (Figure 2).

As seen from Figure 2, a clear linear effect was observed in the asymmetric [6 + 3] cycloaddition of imino ester **2a** with tropone **1** catalyzed by various Cu(I) complex coordinated by ferrocene-based **L7** with varying ee values. Such linear correlation of ee values cycloadduct with that of chiral ligand indicates that the possible active species in the current efficient catalytic system is a monomeric metal complex, which was formed by 1:1 ratio of Cu(I) and the bidentate chiral ligand (S,R_P)-**L7**.[20]

Table 3. Substrate Scope of the Catalytic Asymmetric [6 + 3] Cycloaddition of Tropone 1 with Alkyl Azomethine Ylides 2[a]





[a]All reactions were carried out with 0.24 mmol of **2** and 0.20 mmol of **1** in 1 mL CH_2Cl_2. [b]Isolated yield, and around 15% tropone was recovered. [c]dr was determined by the crude ^1H NMR, and ee was determined by HPLC analysis.

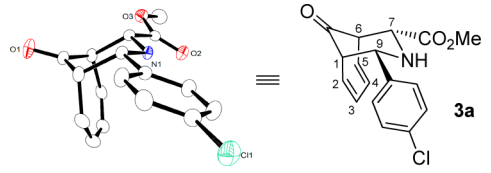


Figure 1. ORTEP representation of (1*S*,6*R*,7*R*,9*S*)-**3a** at 30% probability for the drawing of thermal ellipsoids (hydrogen atoms are omitted for clarity).

A plausible mechanism for this cycloaddition was shown in Scheme 3. The *in situ*-formed azomethine ylide is coordinated to the active Cu complex (**A**) leading to the tetracoordinated species (**B**) based on the linear correlation results. The formation of cycloadduct **3** may be rationalized via a stepwise mechanism: highly steric congestion imposed by the phenyl ring on the phosphorus atom in the chiral ligand effectively blocks tropone (**1**) approach from the upside of the

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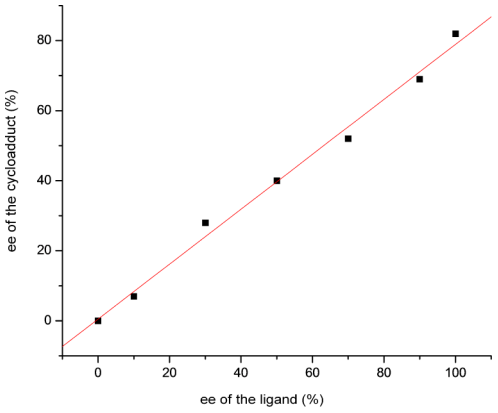
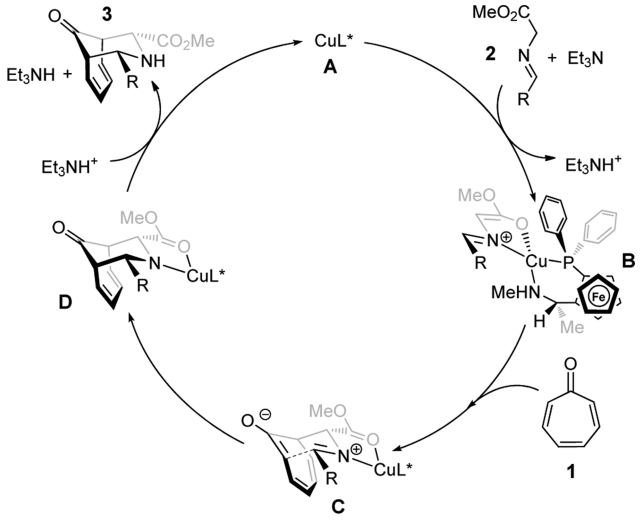


Figure 2. Result of linear effect for the Cu(I)/**L7**-catalyzed [6 + 3] cycloaddition reaction of tropone **1** with **2a**.

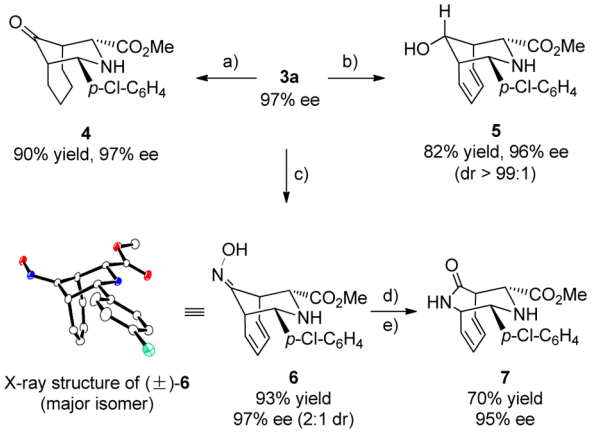
Scheme 3. Plausible Reaction Mechanism



coordinated azomethine ylide, and the initial nucleophilic addition of the metallo-azomethine ylide (**B**) to the α-position of tropone generates the zwitterionic intermediate (**C**). This is followed by intramolecular Mannich addition to yield the species (**D**) containing the bridged azabicyclo[4.3.1]decadiene moiety. Finally, protonation regenerates the catalytically active species **A**. In the six-membered chair-like transition state, the two substituents on the metallo-azomethine ylide are placed at the equatorial positions throughout the intramolecular cyclization step, delivering the cycloadduct **3** with excellent stereoselective control.

Synthetic Transformations and Scale-up Reaction. The optically active bridged-cycloadduct **3a** can serve as synthetically useful precursors for other stereochemically rich structures (Scheme 4). Direct hydrogenation of **3a** in the present of Pd/C afforded **4** in 90% yield. The carbonyl group in **3a** was reduced by $NaBH_4$ in a highly diastereoselective fashion to afford compound **5** containing five consecutive tertiary stereogenic centers in high yield. Additionally, **3a** was successfully converted into oxime **6** in 2:1 ratio, and the relative configuration of the major isomer of oxime **6** was determined by X-ray analysis (see X-ray structure in Scheme 4, hydrogen atoms are omitted for clarity).[19] Subjection of the major isomer of **6**[21] to Beckmann rearrangement provided the

Scheme 4. Synthetic Applications of the Bridged-Cycloadduct 3a[a]

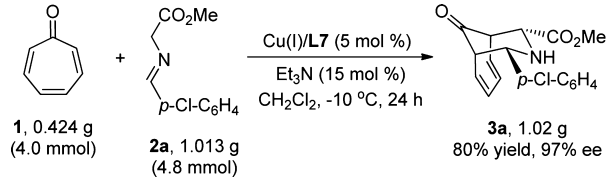


[a]Reaction conditions: (a) Pd/C, H_2, ^{i}PrOH; (b) $NaBH_4$, MeOH; (c) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH; (d) TsCl/DMAP, Et_3N, CH_2Cl_2; (e) MeCN, 65 °C.

lactam **7** in good yield without loss of diastereo-/enantiomeric excess.

In order to further evaluate the synthetic utility of this annulation process, the [6 + 3] cycloaddition reaction was enlarged to a gram scale. Under the optimized reaction conditions, the reaction completed in <24 h, and satisfied results of 80% yield and 97% ee were obtained (Scheme 5).

Scheme 5. Scale-up Reaction



CONCLUSIONS

In summary, we have developed a direct and facile synthesis of bridged azabicyclo[4.3.1]decadiene derivatives, a potentially valuable structural motif for medicinal chemistry. This approach resulted from the development of an unprecedented Cu(I)-catalyzed [6 + 3] cycloaddition reaction of tropone with azomethine ylides. This new asymmetric cycloaddition afforded high yield, complete regioselectivity, and excellent diastereo- and enantioselectivity for imino esters from aryl as well as aliphatic aldehydes. Mechanistic and synthetic studies aiming to understand the origin of catalytic selectivity and to expand the synthetic utility of this asymmetric [6 + 3] cycloaddition are ongoing in this lab. This research work was originally submitted as JACS Communication on July 24th, 2012. When we revised this manuscript as a JACS article, a just accepted manuscript reported the same cycloaddition reaction.[22]

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded on a VARIAN Mercury 300 or 400 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q = quarte, m = multiple or unresolved, brs = broad single, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a

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VARIAN Mercury 75 or 100 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Enantiomeric ratios were determined by HPLC, using chiralpak AS-H and AD-H columns and chiralcel OD-H column with hexane and *i*-PrOH as solvents. Tropone[23] was prepared according to the literature procedure.

General Procedure for Cu(I)-Catalyzed Asymmetric [6 + 3] Cycloaddition of Azomethine Ylides with Tropone. Under argon atmosphere, $Cu(CH_3CN)_4BF_4$ (3.1 mg, 0.010 mmol) and (S,R_P)-**L7** (4.7 mg, 0.011 mmol) were dissolved in 1 mL CH_2Cl_2 and stirred at room temperature for 1 h. Then, aldimino ester **2** (0.24 mmol) and tropone **1** (21 mg, 0.20 mmol) were added sequentially, and the mixture was dropped to −10 °C, and then Et_3N (0.03 mmol, for aryl imino esters) or Cs_2CO_3 (0.4 mmol, for alkyl imino esters) was added. The reaction mixture was stirred at this temperature until the consumption of **1** (monitored by TLC analysis). The residue was purified by flash chromatography on silica gel and gave the corresponding product **3**, which was then directly analyzed by HPLC to determine the enantiomeric excess.

(1*S*,6*R*,7*R*,9*S*)-Methyl 9-(4-chlorophenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (3a, Table 2, entry 1). Yield (76%); White solid, mp: 146 °C; $[\alpha]^{25}_D$ = −84.3 (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.12 (dd, J_1 = 7.6 Hz and J_2 = 11.2 Hz, 1H), 6.00 (dd, J_1 = 7.6 Hz and J_2 = 11.6 Hz, 1H), 5.41 (dd, J_1 = 8.0 Hz and J_2 = 11.6 Hz, 1H), 5.01 (dd, J_1 = 7.6 Hz and J_2 = 11.6 Hz, 1H), 4.37 (m, 1H), 4.15 (dd, J_1 = 4.0 Hz and J_2 = 9.6 Hz 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.63 (m, 1H), 2.29 (t, J_1 = 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 52.4, 55.1, 59.6, 65.0, 65.7, 120.6, 122.1, 127.1, 127.6, 128.3, 128.7, 133.4, 136.7, 169.8, 203.8; IR (KBr) ν 3020, 1634, 1523, 1476, 1424, 1214, 1015, 928, 756, 669 cm^{-1}. HRMS calcd. For $C_{17}H_{16}ClNO_3$: 317.0819, found: 317.0814. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, *i*-propanol/hexane =40/60, flow rate 1.0 mL/min, λ = 220 nm); t_r = 15.02 and 24.92 min.

(1*S*,6*R*,7*R*,9*S*)-Methyl 10-oxo-9-propyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (3s, Table 3, entry 1). Yield (70%); Colorless oil; $[\alpha]^{25}_D$ = +19.3 (*c* 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 6.11−6.06 (m, 2H), 5.52 (m, 1H), 5.29 (m, 1H), 4.02 (d, J = 4.4 Hz, 1H), 3.77 (s, 3H), 3.66 (m, 1H), 3.31 (m, 1H), 3.13 (m, 1H), 1.53−1.40 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) *d* 13.9, 19.4, 35.1, 52.2, 55.8, 57.7, 63.5, 65.7, 120.3, 122.3, 126.7, 127.9, 170.2, 204.3; IR (KBr) ν 3019, 2068, 1635, 1524, 1476, 1424, 1215, 908, 771, 669 cm^{-1}. HRMS calcd. For $C_{14}H_{19}NO_3 + H^+$: 250.1438, found: 250.1441. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, *i*-propanol/hexane =20/80, flow rate 1.0 mL/min, λ = 220 nm); t_r = 17.95 and 23.45 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

cjwang@whu.edu.cn

Notes

The authors declare no competing financial interest.

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