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Metal-Catalyzed [6 + 3] Cycloaddition of Tropone with Azomethine Ylides: A Practical Access to Piperidine-Fused Bicyclic Heterocycles

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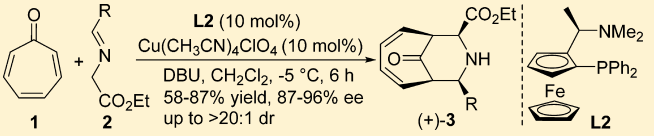
Supporting Information

ABSTRACT: The first metal-catalyzed [6 + 3] cycloaddition of tropone with azomethine ylides has been developed. With the use of a chiral ferrocenylphosphine−copper(I) complex as the catalyst, the asymmetric variant of the [6 + 3] cycloaddition has also been successfully achieved. The reactions proceeded smoothly under mild conditions, affording piperidine-fused bicyclic heterocycles in moderate to high yields with good to excellent diastereo- and enantioselectivies. The procedures are operationally simple and the catalysts are cheap and readily accessible, thus providing a practical approach to piperidine-fused bicyclic heterocycles.

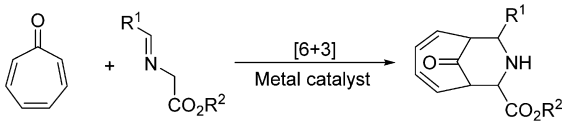


INTRODUCTION

The higher-order cycloaddition has emerged as an efficient and powerful tool for the convergent synthesis of a variety of medium-sized carbo- and heterocycles from a wide range of simpler precursors.[1] Various cycloaddition reactions, such as [4 + 3], [4 + 4], [5 + 2], [5 + 3], [6 + 2], [6 + 3], [6 + 4], [8 + 2], [8 + 3], and so forth, have been developed over the last few decades.[1] Tropones are a class of highly valuable substrates for the cycloaddition reactions,[2] functioning as four-, six-, or eight-member synthons to furnish [4 + 2],[3] [6 + 3],[4] [6 + 4],[5] [8 + 2],[6] or [8 + 3][7] annulation products that are valuable in the synthesis of bioactive molecules[2] and natural products.[3h,4d,5g−i] Although numerous cycloaddition reactions using tropones as reaction partners have been developed, only a few examples involving 1,3-diploar cycloadditions of tropones with dipoles have been reported so far. The early studies on this topic have mostly been focused on the thermal cycloadditions of tropones with dipoles.[3a,5b−d] Recently, Ph_3P-mediated [8 + 2] cycloaddition of tropone with allenic ester/ketone-derived 1,3-dipoles,[6b] Ph_3P-catalyzed [6 + 3][4b] and [8 + 3][7c] cycloadditions of tropone with modified allylic compounds-derived dipoles have also been achieved, providing the corresponding carbo- or heterobicyclic cycloadducts. Concurrently with the preparation of the present manuscript, Ni[7d] and $SnCl_4$[7e]-catalyzed [8 + 3] cycloadditions of tropones with dioples generated from 1,1-cyclopropanediesters were reported, giving functionalized 4,5-dihydrocyclohepta[b]pyran derivatives.

Documented examples on the catalytic enantioselective cycloaddtions of tropones are also quite rare, including Pd-catalyzed asymmetric [6 + 3] cycloaddition of tropones with trimethylenemethane,[4c,d] BINOL-Al-catalyzed asymmetric [4 + 2] cycloaddition of tropones with ketene diethyl acetal,[3g] Ni-catalyzed asymmetric [8 + 3] cycloaddition of tropones with 1,1-cyclopropanediesters[7d] and BINOL-Ti-catalyzed intramolecular [6 + 4] cycloaddition of tropone derivative,[5h] with only a single example of enantioselective catalysis being shown in the last two cases, respectively. To the best of our knowledge, metal-catalyzed [6 + 3] cycloaddition of tropone with azomethine ylides have not yet been reported to date. In the context of our ongoing endeavors in developing 1,3-dipole-based cycloadditions,[8] we explored metal-catalyzed [6 + 3] cycloaddition of tropone with azomethine ylides, which are versatile dipoles in catalytic [3 + 2],[9] [3 + 3][8g,10] and [6 + 3][11] cycloaddition reactions. Herein, we report the first metal-catalyzed [6 + 3] cycloaddition of tropone with azomethine ylides and its asymmetric variant to provide 8-azabicyclo[4.3.1]-deca-2,4-dienes (namely, piperidine-fused bicyclic heterocycles), which are potential scaffolds for the synthesis of natural products[2,12] and biologically important molecules[13] (Scheme 1).

Scheme 1. Metal-Catalyzed [6 + 3] Cycloaddition Reactions of Tropone with Azomethine Ylides



RESULTS AND DISCUSSION

In initial studies, the reaction between tropone (**1**) and the azomethine ylide precursor (**2a**) was surveyed in the presence of 10 mol % of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), using Cu(I) salts as the precatalyst and commercial available and cheap PPh_3 as the ligand. To our delight, under the catalysis of 10 mol % $Cu(CH_3CN)_4ClO_4$ and 20 mol % of

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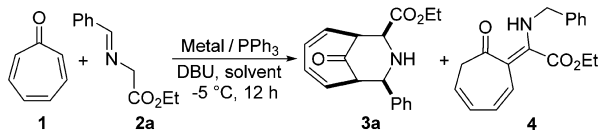
PPh_3, the reaction proceeded smoothly in dichloromethane at −5 °C to give the desired product **3a** as the major product in 56% yield and 2:1 dr, along with a minor amount of the coupling product **4** and an unidentified side product[14] (Table 1, entry 1). The relative configuration of **3a** was assigned by its NMR data and X-ray crystallographic analysis of the corresponding reduction product (+)-**6o** from (+)-**3o**, independently prepared from the cycloaddition of tropone with the α-iminoester **2o** (vide infra).[15] Shifting the solvent to chloroform or methanol revealed that the latter is optimal, resulting in an improved yield to 63% (entries 2−3). Other Cu(I) salts such as CuOAc, CuBr and CuOTf were also found to promote the reaction, albeit in lower yields (entries 4−6). A number of Ag(I) salts (AgOAc, $AgBF_4$, $AgClO_4$, $AgPF_6$, AgF, AgOMs) have also been examined as the catalysts for the reaction under otherwise identical conditions (entries 7−14), among which AgOAc exhibited the best catalytic activity in methanol. In this case, the product **3a** was obtained in 85% yield with 5:1 dr (entry 9). Lowering the reaction temperature further to −20 °C led to an increased yield of **3a** to 91% without loss of the diastereoselectivity, probably as a result of inhibition of byproduct formation (entry 15). Gratifyingly, under the optimized conditions, the reaction could be scaled up to the gram scale (2.12g, 20 mmol of **1**), giving the desired product **3a** in 67% yield (see the Supporting Information for details).

Table 1. Screening of the Reaction Conditions[a]

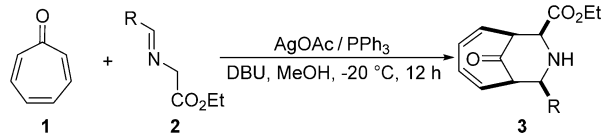


entry	metal	solvent	**3a**/yield [%][b]	**4**/yield [%][b]	dr[c]
1	$CuClO_4$	CH_2Cl_2	56	11	2:1
2	$CuClO_4$	$CHCl_3$	53	trace	3:1
3	$CuClO_4$	MeOH	63	0	5:1
4	CuOAc	MeOH	61	0	4:1
5	CuBr	MeOH	29	6	3:1
6	CuOTf	MeOH	28	0	5:1
7	AgOAc	CH_2Cl_2	45	trace	4:1
8	AgOAc	$CHCl_3$	65	0	5:1
9	AgOAc	MeOH	85	trace	5:1
10	$AgBF_4$	MeOH	33	0	3:1
11	$AgClO_4$	MeOH	39	0	5:1
12	$AgPF_6$	MeOH	32	trace	5:1
13	AgF	MeOH	38	8	3:1
14	AgOMs	MeOH	36	0	7:1
15[d]	AgOAc	MeOH	91	0	5:1

[a]Unless otherwise specified, reactions of **1** (0.3 mmol) and **2a** (0.33 mmol) were carried out at −5 °C in the presence of substoichiometric amounts of the metal salt (0.03 mmol), PPh_3 (0.06 mmol) and DBU (0.03 mmol) in 3 mL of the solvent for 12 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the crude product. [d]The reaction was conducted at −20 °C.

With the optimized conditions in hand, the catalytic [6 + 3] cycloaddition reactions of tropone with a range of α-iminoesters were evaluated using AgOAc/PPh_3 as the catalyst. The results are summarized in Table 2. The procedure worked very well with various α-(benzylideneamino)acetates, irrespective of the stereoelectronic properties of the substituent on the phenyl group, affording the corresponding bicyclic products **3a**−**3u**, a class of 8-azabicyclo[4.3.1]deca-2,4-diene derivatives, in moderate to excellent yields with moderate to excellent diastereomeric ratios (entries 1−21). Unfortunately, aliphatic α-iminoesters were not adaptable substrates for this protocol, probably owing to the strong electron-donating effect of alkyl group that might attenuate the reactivity of the resulting azomethine ylides for cycloaddition reaction.

Table 2. Substrate Scope of Ag-Catalyzed [6 + 3] Cycloaddition of Tropone with Azomethine Ylides[a]



entry	**2**	R	**3**	yield [%][b]	dr[c]
1	**2a**	C_6H_5	**3a**	91	5:1
2	**2b**	2-MeC_6H_4	**3b**	70	6:1
3	**2c**	4-MeC_6H_4	**3c**	63	6:1
4	**2d**	3-$MeOC_6H_4$	**3d**	58	5:1
5	**2e**	2-FC_6H_4	**3e**	85	>20:1
6	**2f**	3-FC_6H_4	**3f**	75	11:1
7	**2g**	4-FC_6H_4	**3g**	70	4:1
8	**2h**	3,4,5−3FC_6H_2	**3h**	67	8:1
9	**2i**	2-ClC_6H_4	**3i**	73	>20:1
10	**2j**	3-ClC_6H_4	**3j**	64	5:1
11	**2k**	4-ClC_6H_4	**3k**	65	>20:1
12	**2l**	2,4−2ClC_6H_3	**3l**	61	>20:1
13	**2m**	2-BrC_6H_4	**3m**	77	>20:1
14	**2n**	3-BrC_6H_4	**3n**	76	5:1
15	**2o**	4-BrC_6H_4	**3o**	68	5:1
16	**2p**	2,5−2BrC_6H_3	**3p**	83	>20:1
17	**2q**	3,4−2BrC_6H_3	**3q**	76	3:1
18	**2r**	3,5−2BrC_6H_3	**3r**	81	17:1
19	**2s**	2-$CF_3C_6H_4$	**3s**	75	>20:1
20	**2t**	3-$CF_3C_6H_4$	**3t**	70	7:1
21	**2u**	4-$CF_3C_6H_4$	**3u**	63	8:1

[a]Reactions of **1** (0.3 mmol), **2** (0.33 mmol), AgOAc (0.03 mmol), PPh_3 (0.06 mmol) and DBU (0.03 mmol) were carried out in 3 mL of MeOH at −20 °C for 12 h. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude product.

Next, we attempted to develop an asymmetric variant of [6 + 3] cycloaddition in the presence of chiral ligand. Some easily accessible chiral ferrocenylphosphine ligands were evaluated for the cycloaddition of **1** with **2a**. The reactions were performed in dichloromethane at −5 °C with a Ag(I) or Cu(I) salt as the precatalyst, and the results were summarized in Table 3. With the use of 10 mol % of **L1**/AgOAc as the catalyst, the reaction of tropone with α-iminoester (**2a**) afforded the product (+)-**3a** in 94% yield with 66% ee and 4:1 dr (entry 1). The absolute and relative configurations as depicted were determined by X-ray diffractional analysis of the reduction product (+)-**6o** derived from chiral product (+)-**3o**.[15] With the use of **L1**/$AgPF_4$ and **L1**/$AgClO_4$ as the catalyst, the enantiomeric excesses were improved to 86% and 78%, but the yields dropped to 40% and 61%, respectively (entries 2, 3). The combination of AgOAc with the commercially available and cheap chiral ligand **L2** was not satisfactory in terms of the moderate enantioinduction (entry 4). Unfortunately, the catalyst **L1**/$CuClO_4$ could only afford trace of the product (entry 5). To our delight, when **L2**/$CuClO_4$ was used as the catalyst, the product (+)-**3a** was obtained in 63% yield with

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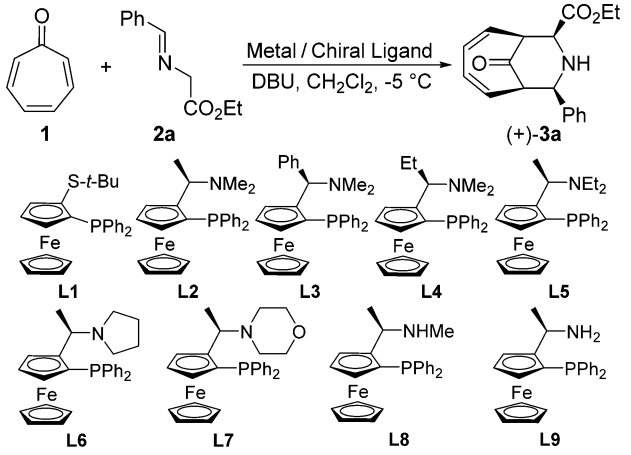
Table 3. Metal-Catalyzed Asymmetric [6 + 3] Cycloaddition of Tropone with Azomethine Ylide[a]



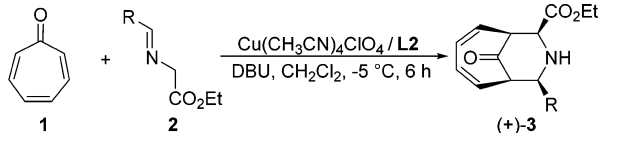
entry	L*	metal	*t*/h	yield (%)[b]	dr[c]	ee (%)[d]
1	**L1**	AgOAc	12	94	4:1	66
2	**L1**	$AgPF_4$	12	40	6:1	86
3	**L1**	$AgClO_4$	12	61	4:1	78
4	**L2**	AgOAc	6	60	2:1	54
5	**L1**	$CuClO_4$	48	trace	-	-
6	**L2**	$CuClO_4$	6	63	7:1	92
7	**L3**	$CuClO_4$	24	trace	-	-
8	**L4**	$CuClO_4$	6	40	4:1	87
9	**L5**	$CuClO_4$	24	45	4:1	79
10	**L6**	$CuClO_4$	24	52	5:1	76
11	**L7**	$CuClO_4$	24	43	4:1	77
12	**L8**	$CuClO_4$	12	47	6:1	61
13	**L9**	$CuClO_4$	24	trace	-	-
14	**L2**	$CuBF_4$	12	45	3:1	90
15	**L2**	CuOAc	12	45	4:1	76

[a]Reactions of **1** (0.1 mmol), **2a** (0.11 mmol), metal salt (0.01 mmol), ligand (0.01 mmol) and DBU (0.01 mmol) were carried out in 1 mL of CH_2Cl_2. [b]Isolated yields. [c]Determined by ^1H NMR analysis of the crude product. [d]Determined by chiral HPLC analysis.

92% ee and 7:1 dr (entry 6). The ferrocenyl P,N ligands **L4**–**L8** bearing a structural skeleton similar to **L2** gave good enantioinduction and moderate yields (entries 8–12), but none of them gave better results than **L2** did. The chiral ligands **L3** and **L9** only resulted in negligible formation of the desired product, respectively (entries 7, 13). When **L2** was used as chiral ligand, other cuprous salts such as $CuBF_4$ and CuOAc were also found to promote the reaction to give the product (+)-**3a** in 90% ee and 76% ee, respectively, albeit in low yields (45%) in both cases (entries 14–15). Finally, the combination of **L2** with $Cu(CH_3CN)_4ClO_4$ was used as the optimal catalytic system for subsequent asymmetric reactions.

Under the optimized reaction conditions, the reactivities of various azomethine ylides derived from the precursors (**2**) were examined for the [6 + 3] cycloadditions with tropone (**1**) (Table 4). When 10 mol % Cu-**L2** was used as the chiral catalyst, the cycloaddition reaction of a series of azomethine ylides with tropone proceeded very well, providing the corresponding chiral 8-azabicyclo[4.3.1]deca-2,4-diene derivatives (+)-**3** in 58–87% yield with 87–96% ee (entries 1–14). The reactions were tolerant of the presence of electron-withdrawing or donating functional groups on the phenyl group of the iminoesters. In particular, 2-fluorophenyl substituted azomethine ylide from the α-iminoester **2e** displayed superior

Table 4. Cu-Catalyzed Asymmetric [6 + 3] Cycloaddition of Tropone with Azomethine Ylides[a]



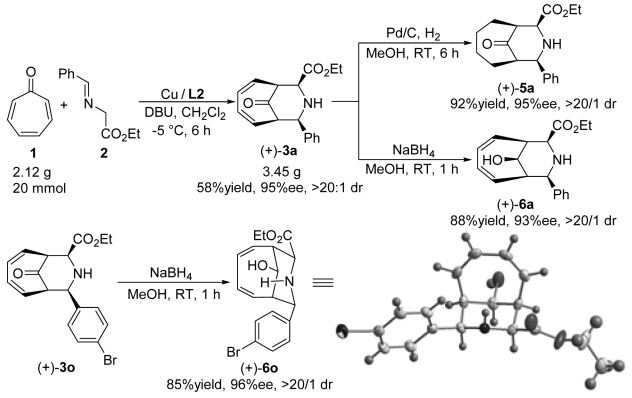
entry	2	R	(+)-3	yield [%][b]	dr[c]	ee [%][d]
1	**2a**	C_6H_5	(+)-**3a**	63	7:1	92
2	**2c**	4-MeC_6H_4	(+)-**3c**	61	5:1	90
3	**2d**	3-MeOC_6H_4	(+)-**3d**	58	8:1	90
4	**2e**	2-FC_6H_4	(+)-**3e**	87	>20:1	95
5	**2f**	3-FC_6H_4	(+)-**3f**	72	6:1	88
6	**2g**	4-FC_6H_4	(+)-**3g**	64	4:1	89
7	**2i**	2-ClC_6H_4	(+)-**3i**	65	>20:1	93
8	**2j**	3-ClC_6H_4	(+)-**3j**	60	5:1	87
9	**2k**	4-ClC_6H_4	(+)-**3k**	60	>20:1	91
10	**2m**	2-BrC_6H_4	(+)-**3m**	71	>20:1	95
11	**2n**	3-BrC_6H_4	(+)-**3n**	70	5:1	90
12	**2o**	4-BrC_6H_4	(+)-**3o**	61	5:1	96
13	**2t**	$3\text{-CF}_3C_6H_4$	(+)-**3t**	65	5:1	88
14	**2u**	$4\text{-CF}_3C_6H_4$	(+)-**3u**	63	>20:1	90

[a]Reactions of **1** (0.1 mmol), **2** (0.11 mmol), $Cu(CH_3CN)_4ClO_4$ (0.01 mmol), **L2** (0.01 mmol) and DBU (0.01 mmol) were carried out in CH_2Cl_2 (1 mL) at −5 °C for 6 h. [b]Isolated yields. [c]Determined by ^1H NMR analysis of the crude product. [d]Determined by chiral HPLC analysis.

reactivity and selectivity, affording the bicyclic product (+)-**3e** in 95% ee and >20:1 dr with 87% yield (entry 4). In contrast, 3-MeO-substituted azomethine ylide gave slightly lower yield (entry 3). Unfortunately, aliphatic azomethine ylides were found unreactive in the reaction under these conditions.

The present asymmetric reaction could be performed on the gram scale with excellent diastereoselectivity and enantioselectivity without significant loss of yield (Scheme 2, see the

Scheme 2. Synthetic Transformations of the Cycloadducts



Supporting Information for details).[16] Furthermore, simple derivatization of the cycloaddition products allows for conversion to several types of valuable chiral bicyclic fused-ring compounds (Scheme 2). For examples, the conjugated diene motif in the product (+)-**3a** was reduced via Pd/C catalyzed hydrogenation to give 8-azabicyclo[4.3.1]decan-10-one derivative (+)-**5a** in 92% yield with 95% ee and >20/1 dr. Alternatively, treatment of (+)-**3a** with $NaBH_4$ in methanol gave the azabicyclo[4.3.1]deca-2,4-dien-10-ol derivative (+)-**6a**

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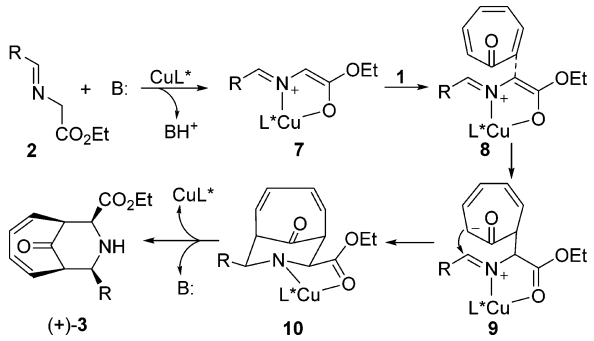
in 88% yield and 93% ee with >20/1 dr. With this procedure, the product (+)-**3o** could also be smoothly reduced to give the corresponding alcohol (+)-**6o** in 85% yield with 96% ee and >20/1 dr. The solid-state molecular structure of (+)-**6o** was determined by single crystal X-ray diffractional analysis, which thus allows for the unambiguous assignment of the absolute configuration of the chiral cycloaddition product (+)-**3** (Scheme 2).[15]

On the basis of previous studies,[3−7] a plausible stepwise mechanism was proposed in Scheme 3 for the Cu(I)-catalyzed

Scheme 3. Proposed Mechanism for the Catalytic Asymmetric [6 + 3] Cycloaddition



cycloaddition of tropone with azomethine ylides. Treatment of **2** with a base in the presence of the in situ generated cuprous complex CuL* would lead to the formation of the metalloazomethine ylide **7** as an active species. The carboxyl enolate cuprous salt **7** might undergo a nucleophilic addition to the electron-deficient tropone to give the zwitterionic intermediate **9** through the transition state **8**. In this case, the steric crowding at the front side of the metalloazomethine ylide **7** would guide the approach of tropone from the backside. Subsequent intramolecular nucleophilic addition to the *si* face of the imine moiety would give the intermediate **10**, which was protonated to accomplish the final [6 + 3] cycloadduct **3** with simultaneous release of the Cu(I) catalyst and the base for next cycle of the reaction.

CONCLUSION

In summary, we have developed the first metal-catalyzed [6 + 3] cycloaddition of tropone with azomethine ylides and its asymmetric variant. The reactions are operationally simple and proceed smoothly under mild conditions, affording piperidine-fused bicyclic heterocycles in moderate to high yields with good to excellent diastereo- and enantioselectivities. Both achiral and chiral catalysts for the reactions are cheap and highly accessible, and moreover, the reactions could be carried out on the gram scale, thus allowing the reaction to be a practical method for the synthesis of piperidine-fused bicyclic heterocycles. Further application of the reaction to asymmetric synthesis of biologically important molecules is underway.

EXPERIMENTAL SECTION

General Information. All reactions were performed under N_2 atm in oven-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Dichloromethane employed in the reactions was freshly distilled from CaH_2. Reactions were monitored through thin layer chromatography (TLC) on silica gel−precoated glass plates. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. Flash column chromatography was performed using Qingdao Haiyang flash silica gel (200−300 mesh). Infrared spectra were recorded using a Bruker Optics TENSOR 27 instrument. ^1H and ^{13}C NMR spectra were recorded using a 300 MHz Bruker instrument (referenced internally to Me_4Si). Chemical shifts (δ, ppm) are relative to tetramethylsilane (TMS) with the resonance of the nondeuterated solvent or TMS as the internal standard. Optical rotation was obtained on an Autopol V Plus polarimeter. HRMS measurements were performed using an Agilent instrument with the ESI-MS technique.

General Procedure for the [6 + 3] Cycloadditions of Tropone 1 and α-Iminoesters 2 Catalyzed by AgOAc/PPh_3 Complex. Under nitrogen atmosphere, PPh_3 (17.60 mg, 0.06 mmol) and AgOAc (5.0 mg, 0.03 mmol) were dissolved in 1 mL of MeOH. The resulting mixture was stirred at −20 °C for about 1 h, followed by sequential addition of tropone **1** (0.3 mmol), α-iminoesters **2** (0.33 mmol), DBU (5.0 μL, 0.03 mmol), and MeOH (2 mL). Upon the completion of the reaction as monitored by TLC, the mixture was concentrated in vacuo. The residue was purified through flash column chromatography (EtOAc/petroleum ether) to afford the corresponding cycloaddition product.

General Procedure for the [6 + 3] Cycloadditions of Tropone 1 and α-Iminoesters 2 Catalyzed by Cu(I)/L2 Complex. Under nitrogen atmosphere, **L2** (4.4 mg, 0.01 mmol) and $Cu(CH_3CN)_4ClO_4$ (3.3 mg, 0.01 mmol) were dissolved in 0.3 mL of CH_2Cl_2. The resulting mixture was stirred at −5 °C for about 1 h, followed by sequential addition of tropone **1** (0.1 mmol), α-iminoesters **2** (0.11 mmol), DBU (1.7 μL, 0.01 mmol) and 0.7 mL of CH_2Cl_2. Upon the completion of the reaction as monitored by TLC, the mixture was concentrated in vacuo. The residue was purified through flash column chromatography (EtOAc/petroleum ether) to afford the corresponding cycloaddition product.

ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(15) Crystallographic data for (+)-**6o** has been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 963393. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

(16) Both the ee and dr values were better than those obtained in the reaction on a 0.1 mmol scale. The reason might be that the reaction on the gram scale was performed with a concentration of 0.05 mol/L of the substrate **1**; in contrast, the reaction on a 0.1 mmol scale was carried out at a substrate concentration of 0.1 mol/L. Interestingly, even if the reaction on a 0.1 mmol scale was carried out at a concentration of 0.05 or 0.025 mol/L, both the ee and dr values could not be increased.