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Asymmetric Synthesis of Bicyclo[4.3.1]decadienes and Bicyclo[3.3.2]-decadienes via [6 + 3] Trimethylenemethane Cycloaddition with Tropones

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The development of new reaction methodologies requiring only a *catalytic* amount of promoter are fundamentally important to the advancement of organic synthesis.[1] Coupled with a mode for enantioinduction, these strategies become indispensable tools for the generation of optically pure molecules in a reasonably atom-economical and environmentally conscious manner. Cycloaddition reactions constitute a special class since such multiple bond-forming processes create much greater molecular complexity than single bond-forming reactions.

The palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane (Pd-TMM) to electron deficient π-systems was introduced almost thirty years ago by our laboratory and constitutes a highly efficient synthesis of substituted cyclopentanes, tetrahydrofurans, and pyrrolidines.[2] Following the initial reports, direct access to bicyclo[4.3.1]decadienes via [6 + 3] TMM cycloaddition to cycloheptatrienones (tropones) was demonstrated to be a highly efficient process.[3] Recently, a new class of chiral phosphoramidite ligands provided a major stimulus to the Pd-TMM reaction by rendering several [3 + 2] cycloadditions enantioselective (Scheme 1).[4] Herein we report the first asymmetric Pd-TMM [6 + 3] cycloaddition of cyanosubstituted TMM substrate **2** with tropones to provide bicyclo[4.3.1]decadienes in high enantiomeric purity.[5] Furthermore, we report their facile thermal rearrangement to yield asymmetric bicyclo[3.3.2]decadienes.

Our studies began with the examination of the Pd-TMM [6 + 3] cycloaddition of donor **2**[4b,6] to 4-carboethoxy-2,4,6-cycloheptatrien-1-one[7] (**3a**; Scheme 1). Using conditions optimized for the [3 + 2] cycloaddition[4,8] we quickly realized high levels of conversion, with bicyclo[4.3.1]decadiene product **4a** as the major constituent. The regiochemistry and relative configuration as depicted were determined by two-dimensional NMR studies and comparison with known [6 + 3] adducts.[3]

Initial efforts to render the reaction enantioselective relied on the commercially available ligand **L1**[9] (Figure 1). Unfortunately, although giving high conversion to product, the enantioselection was rather poor (37% ee). Likewise, phosphoramidite ligand **L2**[9] possessing no chirality in the amine component was largely ineffective for promoting enantioselection. In contrast to these standard phosphoramidites, the cyclic pyrrolidine phosphoramidite ligands **L3**−**5**[4] all gave excellent levels of enantioinduction. Various aryl substituents were examined with bis-(4-biphenyl)phosphoramidite ligand **L5** attaining near perfect enantioselection in 75% isolated yield (see Table 1, entry 1). The excellent behavior of **L5** is somewhat contradictory to previous observations in [3 + 2] cycloadditions demonstrating the efficacy of **L4**.[4c] It is noteworthy that although competing modes of cycloaddition, such as [3 + 2] or [4 + 3], could be envisioned only the [6 + 3] cycloaddition product was obtained. Most remarkably, only one [6 + 3] regioisomer was detectable *and* is generated as a single diastereomer.

On the basis of these promising results, an examination of other tropone systems was undertaken (Table 1). To explore the effect

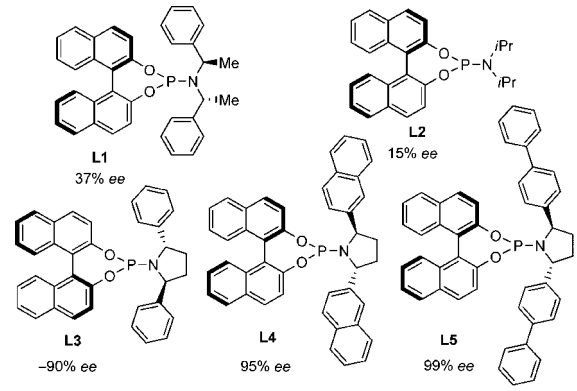
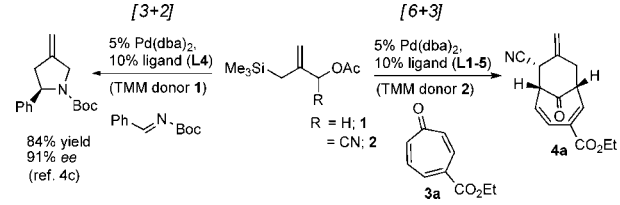


Figure 1. Phosphoramidite ligand screen. Reactions performed at 0.1 M in toluene with 5 mol % $Pd(dba)_2$, 10 mol % ligand, 1.0 equiv **3a**, 1.6 equiv **2**, 0−4 °C for 15 h; ee determined by chiral HPLC.

Scheme 1. Pd-TMM [3 + 2] and [6 + 3] Cycloadditions



of the position of the ester functionality, both the 3-carboethoxy and 2-carboethoxy tropones[7] (**3b**, **3c**) were synthesized. Gratifyingly, both tropones gave comparable reaction yields and excellent diastereo- and enantioselectivity (entries 2 and 3). In both cases, only one [6 + 3] regioisomer was obtained and followed what was predicted from electronic considerations.[10] We also examined less electron deficient tropones, such as tropone (**3d**) itself. Although a higher temperature was required to obtain good conversion, the cycloaddition reaction proceeded to give the desired product **4d** in good yield, diastereomeric ratio, and enantioselectivity (entry 4).

A series of 2-substituted tropones, readily available from tropolone,[11] were also prepared and examined. The reaction of 2-chlorotropone (**3e**) proceeded very well to give the bicycle **4e** in 94% yield and 94% ee (entry 5). X-ray crystallographic analysis on the 2-chloro TMM adduct **4e** unambiguously established both the absolute and relative configuration as depicted. Interestingly, 2-bromotropone failed to give any desired cycloaddition. While 2-methoxytropone also displayed no reactivity, 2-acetoxytropone (**3f**) delivered cycloadduct **4f**, again with excellent yield and enantioinduction (entry 6). Likewise, while 2-dimethylamino tropone was unreactive, 2-phthalimido tropone (**3g**) was well suited to the reaction conditions, although a slightly diminished ee of 86% was observed (entry 7). These results suggest the need for an electron deficient heteroatom to enhance tropone reactivity. In addition, 2-phenyltropone (**3h**) provided cycloadduct **4h** (entry 8)

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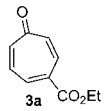
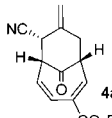
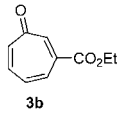
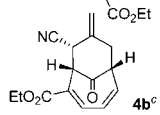
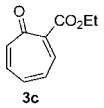
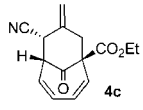
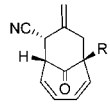
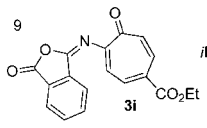
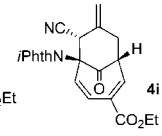
Table 1. Scope of [6 + 3] Pd-TMM Cycloadditions[a]

Entry	Tropone[b]	Product	Yield	d.r.[g]	ee[h]
1	 **3a**	 **4a**	75%[e]	>10:1	99%
2	 **3b**	 **4b**[c]	80%[e]	>10:1	99%
3	 **3c**	 **4c**	77%[e]	>10:1	99%
					
4	R = H; **3d**	R = H; **4d**[d]	89%[f]	6:1	99%
5	R = Cl; **3e**	R = Cl; **4e**	94%[e]	>10:1	94%
6	R = OAc; **3f**	R = OAc; **4f**	90%[e]	>10:1	96%
7	R = NPhth; **3g**	R = NPhth; **4g**	85%[e]	>10:1	86%
8	R = Phenyl; **3h**	R = Phenyl; **4h**[c]	64%[f]	6:1	93%
9	 **3i**	 **4i**	78%[f]	3:1	91%[i]

[a] All reactions performed at 0.2−0.25 M in toluene with 5 mol % $Pd(dba)_2$, 10 mol % ligand **L5**, 1.6 equiv donor **2**, 0−4 °C for 15 h. [b] See Supporting Information for tropone syntheses. [c] Reaction at room temp. [d] Reaction at 45 °C. [e] Isolated yield of major diastereomer. [f] Isolated yield of both diastereomers. [g] Determined by NMR analysis of the crude reaction mixture. [h] Determined by chiral HPLC. [i] Of major diastereomer.

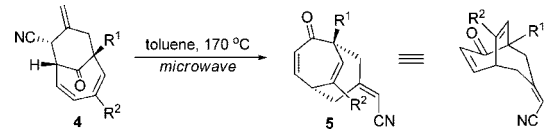
in good yield and stereoselectivity. It is interesting to note that regardless of the electronic nature of the 2-substituted tropones, exclusive regioselectivity for the products bearing the cyano group opposite to the substituent is observed. This regiochemical independence may be supportive of a concerted mechanism, an aspect of these cycloadditions that remains debatable.[2,12]

To examine the directing effects of multiple substituents, 2-amino-4-carboethoxy tropone was prepared. Not surprisingly, use of the phthalimido protecting group at C2 led to a mixture of regioisomers. However, upon changing to isophthalimido tropone **3i** excellent regioselectivity was attained. Unlike previous examples, the diastereomeric ratio was lower, but high ee was still observed for the major diastereomer **4i** (entry 9).

An examination of the 3-dimensional structure of the TMM adducts revealed the proximity of the exocyclic olefin to the endocyclic diene. Thus, it was anticipated that a [3,3] sigmatropic (Cope) rearrangement may be induced to convert the bicyclo[4.3.1]decadiene to a bicyclo-[3.3.2]decadiene in a stereodefined manner. Such a process would then provide a facile, two-step asymmetric synthesis of a rather unique functionalized bicyclic motif. In the event, simply heating the TMM adducts (**4a**, **4d**, and **4f**) in toluene under microwave conditions gave good yields of the rearrangement products (**5a**, **5d**, and **5f**; Table 2).[13] To verify chirality transfer during the reaction, TMM adduct **4d** of 99% enantiomeric excess was converted to the [3.3.2]bicycle **5d** while maintaining an ee of 98%. Presumably, rearrangement products **5a** and **5f** retained full stereochemistry as well.

In conclusion, an enantioselective palladium-catalyzed trimethylenemethane cycloaddition reaction with tropones has been developed,

Table 2. Cope Rearrangements



TMM adduct	product	yield[a]	ee[b]
4a	R^1 = H, R^2 = CO_2Et; **5a**	75%	n.d.
4d	R^1, R^2 = H; **5d**	72% (85%)	98%
4f	R^1 = OAc, R^2 = H; **5f**	72% (86%)	n.d.

[a] Isolated yield, yield in parenthesis is based on recovered starting material. [b] ee determined by chiral HPLC; n.d. = not determined.

providing access to asymmetric substituted bicyclo[4.3.1]decadienes in a single operation. In almost all cases where cycloaddition proceeded, extremely high regio-, diastero-, and enantiocontrol was observed. The complete preference for [6 + 3] cycloaddition, especially in cases where [3 + 2] cycloaddition could be anticipated (tropones **3a**, **3b**, and **3c**) is an intriguing aspect. Additionally, the facile thermal rearrangement of the TMM adducts greatly expands the utility of this methodology by allowing access to bicyclo[3.3.2]decadienes in a straightforward manner.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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