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Asymmetric Synthesis of Bicyclo[4.3.1] and [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-cyclohepatrien-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.

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Based on these promising results, an examination of other tropone systems was undertaken (Table 1). To explore the effect 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) 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 exo-cyclic 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, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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5. An intramolecular asymmetric [6+4] cycloaddition to a tropone (40% *ee*) has been reported: Rigby JH, Fleming M. Tetrahedron Lett 2002;43:8643.
6. Use of donor **1** led to an intractable mixture of cycloaddition products. Work in this area is ongoing.
7. (a)See supporting information for tropone syntheses. Isakovic L, Ashenhurst JA, Gleason JL. Org Lett 2001;3:4189. [PubMed: 11784174]and references therein
8. Optimized reaction conditions employed 5 mol% $Pd(dba)_2$, 10 mol% ligand, and 1.6 equivalents donor **2** in toluene at 0 °C for 15 h. $Pd_2(dba)_3$-$CHCl_3$ complex (2.5 mol%) gave identical reactivity.
9. Feringa BL. Acc Chem Res 2000;33:346. [PubMed: 10891052]
10. For a discussion on the regioselectivity of [6+4] cycloadditions to tropones see: Garst ME, Roberts VA, Houk KN, Rondan NG. J Am Chem Soc 1984;106:3882.
11. (a) Doering, WvE; Knox, LH. J Am Chem Soc 1951;73:828. (b) Doering, WvE; Knox, LH. J Am Chem Soc 1952;74:5683. (c) Doering, WvE; Hiskey, CF. J Am Chem Soc 1952;74:5688.
12. Singleton DA, Schulmeier BE. J Am Chem Soc 1999;121:9313.
13. In contrast to our flexible system, a rigidly held 1,5-diene undergoes a similar rearrangement at room temperature: (a) Paddon-Row MN, Warrener RN. Tetrahedron Lett 1974;15:3797. (b) Tegmo-Larsson I, Houk KN. Tetrahedron Lett 1978;19:941.

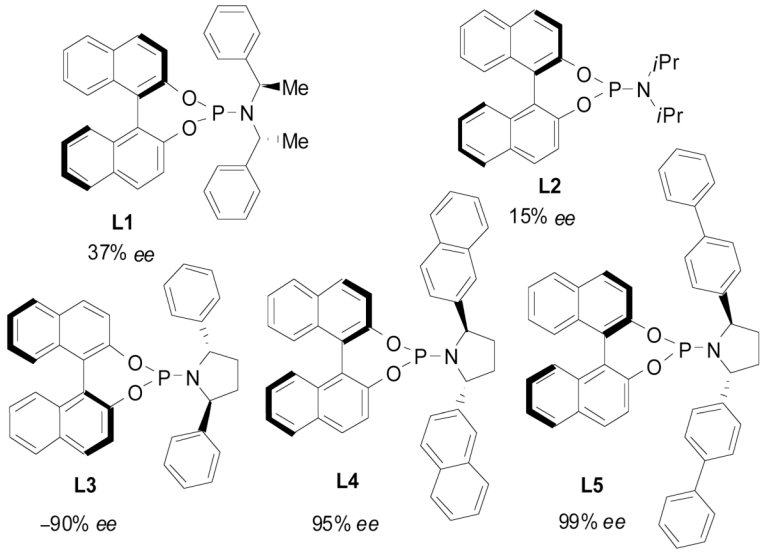
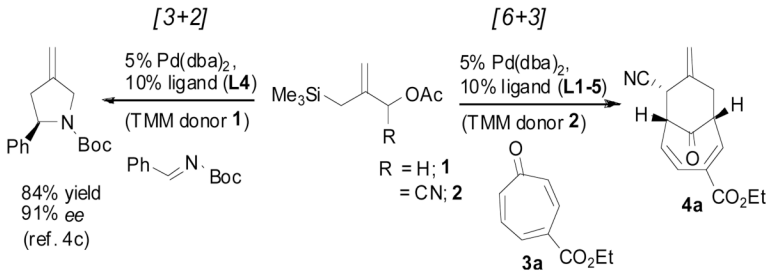
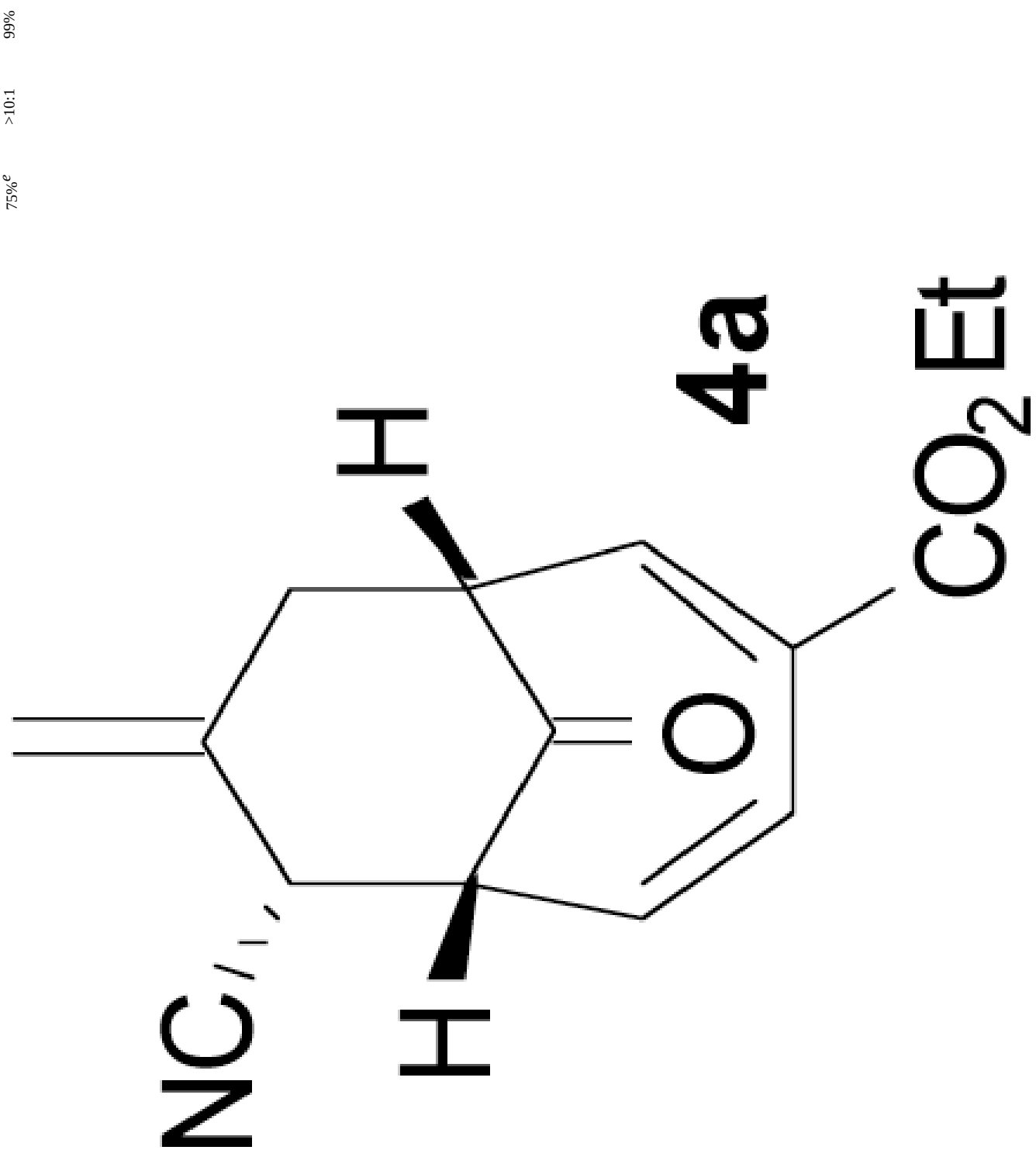


Figure 1.
Phosphoramidite Ligand Screen[a]
[a] Reactions performed at 0.1 M in toluene with 5 mol% $Pd(dba)_2$, 10 mol% ligand, 1.0 equiv. **3a**, 1.6 equiv. **2**, 0-4 °C for 15 h. *ee* determined by chiral HPLC.



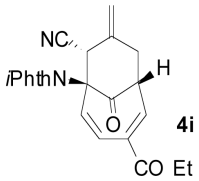
Scheme 1.
Pd-TMM [3+2] and [6+3] Cycloadditions

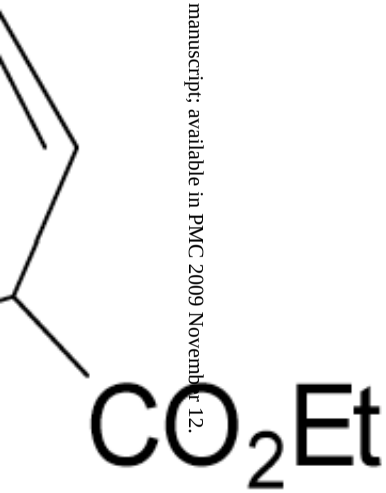
Table 1

Product	Yield	d.r.[g]	ee[h]
	75%[e]	>10:1	99%

Product	Yield	d.r.[g]	ee[h]
4b[c]	80%[e]	>10:1	99%

Product	Yield	d.r.[g]	ee[h]
4c	77%[e]	>10:1	99%

Product	Yield	d.r.[g]	ee[h]
R = H; **4d**[d]	89%[f]	6:1	99%
R = Cl; **4e**	94%[e]	>10:1	94%
R = OAc; **4f**	90%[e]	>10:1	96%
R = NPhth; **4g**	85%[e]	>10:1	86%
R = Phenyl; **4h**[c]	64%[f]	6:1	93%
 **4i**	78%[f]	3:1	91%[i]



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h.

[b] See supporting information for tropone syntheses.

[c] Reaction at r.t.

[d] Reaction at 45 °C.

[e] Isolated yield of major diastereomer.

[f] Isolated yield of both diastereomers.

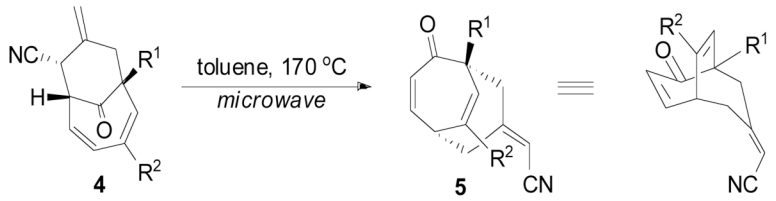
[g] Determined by NMR analysis of the crude reaction mixture.

[h] Determined by chiral HPLC.

[i] Of major diastereomer.

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.