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Enantiocontrolled Synthesis of Highly Functionalized Tropanes via [5 + 2] Cycloaddition to η^3-Pyridinylmolybdenum π-Complexes

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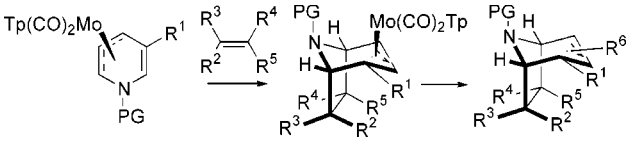
ABSTRACT



A chiral, nonracemic η^3-pyridinyl scaffold participates in [5 + 2] cycloaddition with electron-deficient alkenes, an allene, and an alkyne to give η^3-allylmolybdenum bicyclic adducts. The adducts can be demetalated, providing a convergent route to highly functionalized tropanes. High enantiocontrol can be achieved throughout the cycloaddition and demetalation sequence.

The psychostimulatory effects of cocaine and related alkaloids render compounds possessing the azabicyclo [3.2.1]-octane (tropane) skeleton attractive synthetic targets.[1] Although several asymmetric syntheses of tropanes have recently been reported,[2] the regio- and *enantiocontrolled* introduction of various substituents around the tropane skeleton remains a challenging problem.[3] An expedient solution to this problem draws precedence from a previously described enantiocontrolled construction of oxabicyclo[3.2.1]-octenes[4] and arises from the [5 + 2] attachment of various unsaturated building blocks to a single face of the chiral, nonracemic pyridinyl scaffold **I** (Figure 1). The $TpMo(CO)_2$ auxiliary of **I** (Tp = hydridotris(1-pyrazolyl)borate) has been shown to constitute an ideal metal−ligand set capable of mediating *multiple* and *sequential* regio- and stereoselective functionalizations of various π-substrates.[4−6] Therefore, if chiral, nonracemic $TpMo(CO)_2$(pyridinyl) complexes **I** could be prepared, substituted tropane alkaloids **III** would result from demetalation−functionalization of the [5 + 2] adduct **II**. Described herein is a general, convergent, and enantiocontrolled synthesis of functionalized tropanes based on the above outlined strategy. Related cycloadditions of pyridinium betaines ([5 + 2])[7] and racemic furan and pyrrole-derived π-complexes ([4 + 2]) are known.[8]

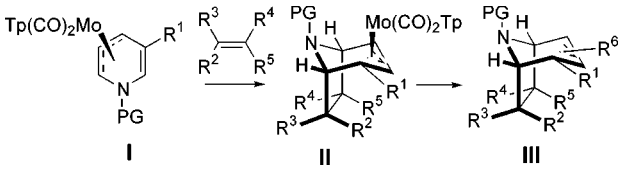


Figure 1. Tropane synthetic strategy.

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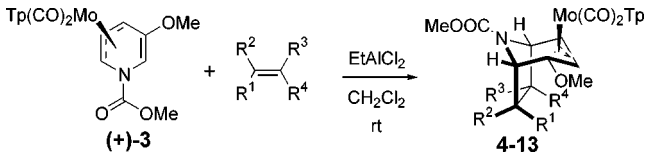
Table 1. [5 + 2] Cycloaddition of η^3-Pyridinylmolybdenum π-Complexes

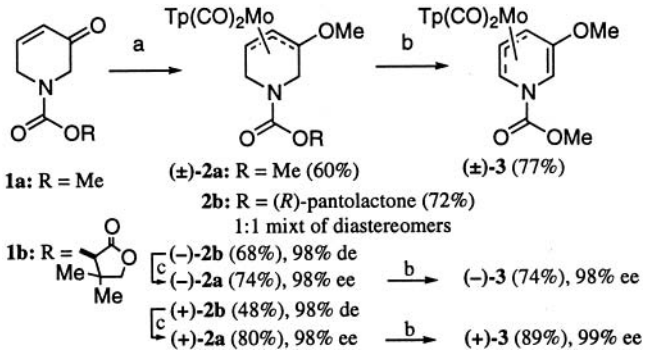


entry	alkene	conditions[a]	yield, exo:endo	prodt	R^1	R^2	R^3	R^4	% ee
1	*N*-methylmaleimide	120%, 10 min	68%, 100:0	**4**	H	−CON(Me)CO−		H	*b*
2	CH_2=CHCOMe	50%, 20 min	79%, 82:12	*exo*-**5a**	H	H	COMe	H	*b*
				endo-**5b**	H	H	H	COMe	*b*
3	2-cyclohexenone	50%, 30 min	87%, 100:0, 8% recov **3**	**6**	H	−$(CH_2)_3$CO−		H	97[c]
4	CH_2=$CHCO_2$Me	180%, 55 min	88%, 100:0, 5% recov **3**	**7**	H	H	CO_2Me	H	98[c]
5	CH_2=C(Me)CO_2Me	150%, 16 h	47%, 100:0, 21% recov **3**	**8**	H	H	CO_2Me	Me	65[d]
6	CH_2=C(Me)CHO	20%, 40 min	74%, 61:39, 21% recov **3**	*exo*-**9a**	H	H	CHO	Me	95[c]
				endo-**9b**	H	H	Me	CHO	95[c]
7	(*E*)-EtCH=CHCHO	40%, 40 min	74%, 57:43, 14% recov **3**	*exo*-**10a**	Et	H	CHO	H	*b*
				endo-**10b**	H	Et	H	CHO	*b*
8		180%, 16 h	86%, 69:31	*exo*-**11a**	H	H	−$CO_2(CH_2)_2$−		*b*
				endo-**11b**	H	H	−$(CH_2)_2O_2C$−		*b*
9	MeO_2CCH=C=$CHCO_2$Me	110%, 35 min	57%	**12**	=$CHCO_2$Me	CO_2Me	H		*b*
10	HC≡CCO_2Et	150%, 2.5 h	68%, 11% recov **3**	**13**	H	C−C bond		CO_2Et	*b*

[a] Mol % $EtAlCl_2$, time. [b] rac-form was used. [c] (−)-**3** of 98% ee was used. [d] (+)-**3** of 96% ee was used.

Racemic and chiral, nonracemic pyridinylmolybdenum complexes were prepared by the reaction sequence depicted in Scheme 1. Complex (±)-**2a**, which is readily available

Scheme 1. Synthesis of $Tp(CO)_2Mo$(pyridinyl) Scaffolds of High Enantiopurity[a]



[a] (a) (i) $Mo(CO)_3(DMF)_3$, TBDMSCl; (ii) KTp; (iii) TBAF; (iv) MeI; (b) (i) Ph_3CPF_6; (ii) TEA; (c) (i) SmI_2, HMPA, MeOH; (ii) $ClCO_2Me$, 3 N aqueous NaOH.

from (±)-**1a** by following an established procedure,[6] was transformed into racemic (±)-**3** upon sequential treatment with Ph_3CPF_6 and Et_3N. An analogous sequence starting with pyridone **1b** afforded complex **2b**, armed with an (*R*)-pantolactone-derived chiral auxiliary. Although formation of **2b** did not proceed with asymmetric induction, diastereomerically pure (−)-**2b** (98% de) and (+)-**2b** (98% de) were conveniently obtained in good yields on a large scale (14 and 7.8 g of pure diastereomers) after two crystallizations. X-ray crystallographic analysis of (−)-**2b** permitted the assignment of absolute configuration for complexes **2b** and all the products later derived from them. While numerous standard protocols[9] failed to cleanly remove the chiral auxiliary in **2b**, SmI_2-induced deoxygenation[10] of the α-carbamyloxy lactone followed by treatment of the free base with methoxychloroformate furnished both antipodes of **2a** (74% and 80% yields, 98% ee), which were subsequently converted into (−)-**3** (74% yield, 98% ee) and (+)-**3** (89% yield, 99% ee)[11] with Ph_3CPF_6 and Et_3N.

Unsaturated moieties activated by various electron-withdrawing groups afforded the [5 + 2] cycloadducts **4**−**13** shown in Table 1 in good to excellent yields (47%−88%) and with good exo:endo selectivities (4:3−1:0). As anticipated from previous studies,[4] Lewis acid ($EtAlCl_2$) was required to initiate the [5 + 2] cycloaddition. The examples depicted in Table 1 demonstrate the broad scope of the

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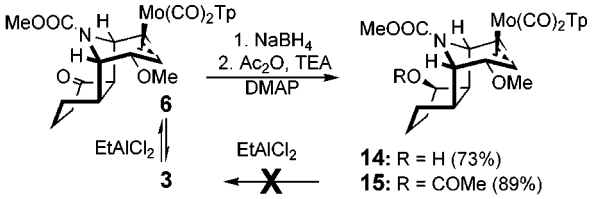
(11) Partial racemization of (−)-**3** (to 94% ee in one case) can be prevented by limiting all solution manipulations of **3** including chromatography. A brief study revealed (i) slow racemization of ethanolic solutions of **3** at room temperature exposed to light, (ii) no racemization in the dark, and (iii) in the dark, racemization was induced by the addition of a Lewis acid ($Sc(OTf)_3$) to ethanolic solutions of **3**.

reaction with respect to olefins bearing alkyl substituents on α- or β-carbons (trisubstituted olefins did not react). Facile additions to an exocyclic double bond in α-methylene-γ-butyrolactone (entry 8) and to an allene (entry 9) are especially notable. Most importantly, cycloadducts can be prepared in high enantiomeric excess (95−98%). Although a potential pathway for racemization of **3** is available,[4,11] the cycloaddition is apparently faster than racemization of complex **3** under the reaction conditions. Only the cycloadduct **8**, derived from a poorly reactive methyl methacrylate in a slow reaction, was obtained in a low optical purity (entry 5, 65% ee). X-ray crystallographic analysis of complexes **5a**, **8**, **9b**, **10a**, **12**, and **15** allowed assignment of the structures and confirmed the anticipated formation of new C−C bonds from the face opposite the metal−ligand moiety.[12]

The following observations were noteworthy: $EtAlCl_2$ used in excess, as well as prolonged reaction times, lowered the yields of cycloadducts and decreased the exo:endo selectivity. The yield of cycloadduct **6** (87%) could not be further improved, even though unreacted complex **3** was recovered (entry 3, Table 1). These observations are suggestive of a readily reversible, Lewis acid mediated [5 + 2] cycloaddition. In fact, when cycloadducts **5a**, **6**, and **9a** (Table 1) were exposed to $EtAlCl_2$ (50 mol %, 4−6 h, room temperature), mixtures containing both the exo and endo cycloadducts and the cycloreversion complex (±)-**3** were generated. In contrast, cycloadducts **7** and **8** (Table 1) were stable (16 h) in the presence of excess $EtAlCl_2$ (150 mol %). Furthermore, reduction of readily reversible cycloadduct **6** followed by acetylation of alcohol **14** furnished the modified cycloadduct **15**, which was stable in the presence of excess $EtAlCl_2$ (Scheme 2). Thus, the functional group

Scheme 2. Effect of Functional Groups on Cycloadduct Stability

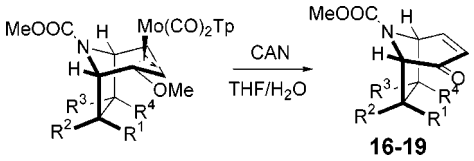


present in the cycloadducts **4**−**13** determines the stability, possibly reflecting the tendency for a Lewis acid induced C_5−C_6 bond cleavage leading to a stabilized zwitterionic intermediate prior to cycloreversion.[13] The equilibrium could not be significantly shifted in favor of products by decreasing the reaction temperatures (−78 °C).

Ceric ammonium nitrate (CAN)-mediated oxidative demetalation[4] concluded the synthetic sequence (Table 2).

(12) Structure assignments for the remaining cycloadducts were based on ^{1}H NMR spectra. The coupling constants for protons H_1 and H_5 adjacent to the bridging nitrogen were indicative of the exo and endo relationships. The structure of adduct **11a** was arbitrarily assigned as exo by relying on the demonstrated (X-ray) preference for the exo adducts.

Table 2. Demetalation of the [5 + 2] Cycloadducts



	substrate	prdt (%)	R^1	R^2	R^3	R^4	ee%
1	**4**	**16** (52%)	H	-CON(Me)CO-		H	
2	**6** or (−)-**6**	**17** (81%)	H	−$(CH_2)_3$CO−		H	96[a]
3	**7** or (−)-**7**	**18** (77%)	H	H	CO_2Me	H	98[b]
4	**9a**	**19** (77%)	H	H	CHO	Me	

[a] Prepared from (−)-**6** of 97% ee. [b] Prepared from (−)-**7** of 98% ee.

Cycloadducts featuring a range of functional groups efficiently afforded racemic tropanes **16**−**19** and also tropanes **(+)-17** and **(+)-18** in high enantiomeric purity (96 and 98% ee). The enones **16**−**19** are well suited for further synthetic manipulations.[1]

In conclusion, an enantiocontrolled [5 + 2] cycloaddition of a pyridinyl-based $TpMo(CO)_2$ scaffold has been described. The method provides a convergent access to tropanes with substituent patterns that are difficult to obtain by other methods. Tropanes of high enantiomeric purity (95−98% ee) were prepared using this method, and both optical antipodes are equally accessible. Application of this chemistry to the enantiocontrolled synthesis of spirooxindole alkaloids is currently under investigation. The generation of tropane diversity libraries is an obvious extension of this new reaction.

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Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study and X-ray crystallographic studies of adducts (−)-**2b**, **5a**, **8**, **9b**, **10a**, **12**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The analogous reaction leading to oxabicyclo[3.2.1]octenes proceeds through the zwitterionic intermediate **IVa**.[4] The reversibility of some of the cycloadditions reported here lend credence to a path proceeding through zwitterionic intermediate **IVb**.