Enantioselective Synthesis of a 1,2-Disubstituted Mitosene by a Copper-Catalyzed Intramolecular Carbon–Hydrogen Insertion Reaction of a Diazo Ester

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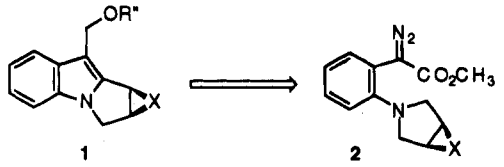
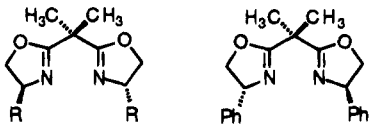
In connection with synthetic and mechanistic investigations of the antitumor agent FR-900482, we contemplated a synthesis of 1,2-disubstituted mitosenes (cf. **1**).[1,2] The disconnection **1** → **2** is particularly appealing since diazo ester **2** is a meso compound and in the forward sense an asymmetric intramolecular C–H insertion followed by oxidation could deliver **1** enantioselectively. Furthermore the carbon–hydrogen insertion process may be facilitated by favorable conformational and electronic effects.



1 **2**

Considerable effort has been expended on the development of asymmetric carbon–hydrogen insertion reactions involving various chiral rhodium(II) catalysts.[3] To the best of our knowledge, however, chiral copper(I) catalysts have not been used. The reason for this disparity is that rhodium(II) carboxylates are generally thought to give superior selectivities and reactivities compared with their copper(I) counterparts.[4] Herein we report preliminary investigations using chiral bis(oxazoline) copper(I) catalysts in the intramolecular C–H insertion reaction of diazo esters **7a** and **7b**.[5,6] These studies imply that chiral copper catalysts may actually be superior to rhodium catalysts in some situations.

Diazo ester **7a** was prepared in six steps from 2-nitrophenylacetic acid (**4**) as outlined in Scheme 1.[7–9] Intramolecular carbon–hydrogen insertion of the carbenoid derived from **7a** may occur at one of four C–H bonds adjacent to the nitrogen heteroatom. These hydrogens consists of two sets of diastereotopic methylene hydrogens



3a R = $CH(CH_3)_2$
3b R = $C(CH_3)_3$ **3c**

reflected through a mirror plane. The diastereotopic hydrogens differ in endo and exo orientation relative to the neighboring acetonide group. Insertion into the exo C–H bond leads to the anti isomer **8** while insertion into the endo C–H bond will provide the syn isomer **9**. Alternatively, carbenoid insertion into the other set of diastereotopic methylene hydrogens will afford the enantiomers of **8** and **9** (not shown). Finally, the C9 carbomethoxy group may adopt an exo (**8a** and **9a**) or endo (**8b** and **9b**) orientation. Oxidation of isomers **8** and **9** provides the 1,2-disubstituted mitosene **10**.

Enantioselective formation of mitosene **10** was investigated using the following procedure. Diazo ester **7a** was added via syringe pump to a solution of catalyst over the time indicated in Table 1. After completion of the reaction (TLC), diastereomers **8** and **9** were separated and individually subjected to DDQ oxidation to give **10**. In these experiments exo and endo isomers were not separated but directly oxidized to mitosene **10** and the enantiomeric excess of **10** determined by ^1H NMR using the chiral lanthanide shift reagent Eu(hfc)$_3$.

The initial experiments in this study were performed using some rhodium catalysts. Rhodium(II) acetate catalyzed decomposition of **7a** in dichloromethane at room temperature (entry 1). Under these conditions **7a** produced a 1:1 mixture of **8** and **9** as a 10:1 and 3:1 mixture of exo and endo esters (**8a/8b** and **9a/9b**), respectively.[7] Structural assignments were based upon NOE studies of **8b** and **9b**. Attempts to induce asymmetry using chiral rhodium(II) catalysts Rh_2(5(*S*)-MEPY)$_4$ and Rh_2((*S*)-TBSP)$_4$ provided discouraging results (entries 2 and 3).[3a,c,e] The former catalyst provided only racemic products presumably derived from the thermal (uncatalyzed) decomposition of **7a**.

Bis(oxazoline) copper(I) complexes were made from the addition of the indicated ligand (**3**) to a suspension of copper(I) triflate in dichloromethane. The isopropyl and *tert*-butyl ligands (**3a** and **3b**) provided products **8** and **9** in a ratio of 2:1 (entries 4 and 8). Individual oxidation of **8** and **9** derived from the isopropyl series produced **10** in 18 and 20% enantiomeric excess (entry 4). While the corresponding isomers (**8** and **9**) produced in the *tert*-butyl series yielded **10** in enantiomeric excesses of 20 and 16% (entry 8), the phenyl-derived ligand led to no improvement in diastereo- or enantioselectivity (entry 10).

Reactions using chloroform as a solvent provided superior diastereo- and enantioselectivity, while no improvement was observed using acetonitrile or benzene (entries 6 and 7). For example, addition of a chloroform solution of diazo ester **7a** to a mixture of Cu(I)•**3a** afforded **8** and **9** in a 3:1 ratio and a combined yield of 94% yield (entry 5). Oxidation of these products provided **10** in enantiomeric excesses of 48 and 20%, respectively.[10] *Interestingly, not only did the diastereo- and enantioselectivity increase relative to the reaction using dichlo-*

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(7) The structure assigned to each new compound was in accord with its infrared, 200-MHz ^1H NMR, and 50 MHz ^{13}C NMR spectra, as well as appropriate parent ion identificaton by high-resolution mass spectrometry and/or elemental composition analysis.

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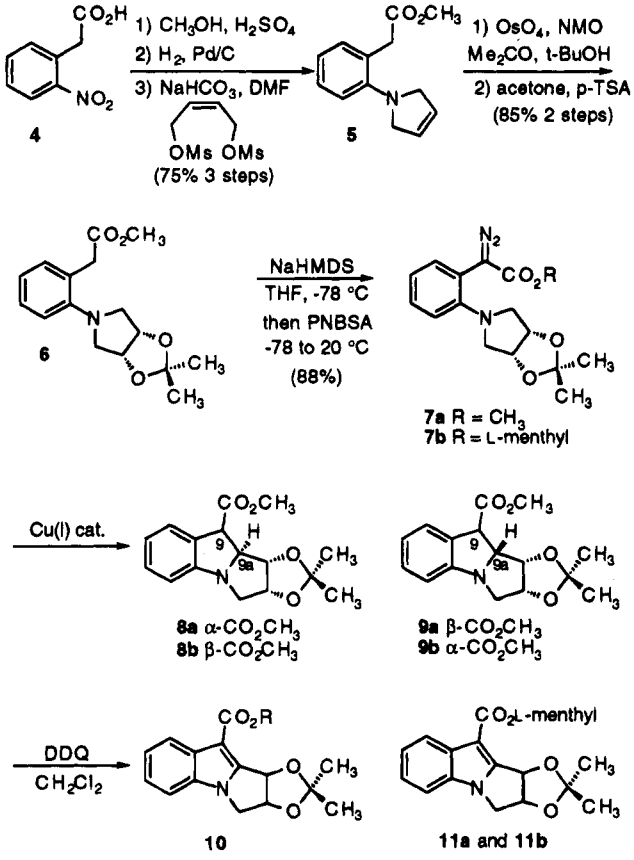
Table 1. Diastereo- and Enantioselectivity of Carbon–Hydrogen Insertion Reaction of Diazo Ester 7a

entry	catalyst[c]	solvent	time (h)	% yield	8:9	8a:8b	9a:9b	% ee ($[\alpha]^{25}_D$) 10[a]	% ee ($[\alpha]^{25}_D$) 10[b]
1	$Rh_2(OAc)_4$	CH_2Cl_2	7	95	1:1	10:1	3:1		
2	$Rh_2(5(S)\text{-MEPY})_4$	CH_2Cl_2	17[g,h]	88	1.6:1	<5:95[e]	<5:95[f]		
3	$Rh_2((S)\text{-TBSP})_4$	CH_2Cl_2	17[g]	95	1.5:1	10:1	3:1	10 (+20.4)	11 (+22.4)
4	Cu(OTf)·**3a**	CH_2Cl_2	6	85	2:1	2:1	1:1	18 (+38.3)	20 (+42.5)
5	Cu(OTf)·**3a**	$CHCl_3$[i]	14	94	3:1	1:1	2:1	48 (−104.6)	20 (−42.5)
6	Cu(OTf)·**3a**	CH_3CN[i]	12[j]	60	1:2			12 (+25.0)	12 (+25.0)
7	Cu(OTf)·**3a**	C_6H_6[i]	12[j]	33 (47)[d]	2:1			11 (−22.8)	3 (−6.0)
8	Cu(OTf)·**3b**	CH_2Cl_2	17	76	2:1	1:1	9:1	20 (+43.1)	16 (+33.8)
9	Cu(OTf)·**3b**	$CHCl_3$[i]	12[j]	57	5:1	1:1	1:1	26 (−53.3)	0
10	Cu(OTf)·**3c**	CH_2Cl_2	15	87	2:1	1:2	13:1	6 (−12.8)	15 (−31.9)
11	Cu(OTf)·**3c**	$CHCl_3$[h]	14	92	3:1	1:5.5	2:1	37 (+79.0)	25 (+53.0)

[a] Derived from **8**. [b] Derived from **9**. [c] 10 mol % catalyst. [d] Based on recovered starting material. [e] Endo ester **8b** only observed by ^{1}H NMR. [f] Endo ester **9b** only observed by ^{1}H NMR. [g] The reaction was maintained at reflux. [h] Stirred for an additional 18 h at reflux following completion of the addition of **7a**. [i] 4-Å molecular sieves were added.[10b] [j] Reaction mixture stirred for an additional 30 h at room temperature following completion of the addition of **7a**.

Scheme 1



*romethane as a solvent but the sense of asymmetric induction reversed, the levorotatory isomer (−)-**10** now predominating.*[10b] Examination of Table 1 shows that this is a general phenomenon (entries 8–11). *A second notable observation is that the anti and syn isomers (**8** and **9**) in each case yield an excess of the same antipode so the insertion predominately occurs at one of the two sets of diastereotopic methylene hydrogens throughout.* Use of the more sterically demanding *tert*-butyl ligand **3b** gave a diminished chemical and optical yield (entry 9). Finally, the phenyl ligand **3c** provided results comparable to those of the isopropyl series (entry 11).

Enantioselectivities of C–H insertion reactions and cyclopropanations of olefins using diazo esters have been enhanced by alteration of the alkoxy group.[5b,11] In this study, menthyl ester **7b** in the presence of rhodium(II) acetate gave a 1:1 mixture of diastereomers **11a** and **11b** after DDQ oxidation. Unfortunately, we were unable to assign the relative configurations of **11a** and **11b**. Next, we examined the cyclization of **7b** using the copper catalysts derived from (*S,S*)-**3a** and (*R,R*)-**3c** [chloroform solvent, 4-Å molecular sieves]. Carbon–hydrogen insertion mediated by Cu(I)·**3a** followed by DDQ oxidation produced the chromatographically less mobile isomer in 34% de (66% isolated yield), while decomposition of diazo ester **7b** with Cu(I)·**3c** followed by oxidation afforded the other isomer in 39% de (64% isolated yield). Isomers **11a** and **11b** were then individually correlated with methyl ester **10** by saponification followed by diazomethane esterification. The major isomer produced from Cu(I)·**3a** provided the levorotatory isomer {$[\alpha]^{20}_D$ −207.9° (*c* 0.3, CH_2Cl_2)}, while the minor isomer yielded the dextrorotatory isomer {$[\alpha]^{20}_D$ +212.7° (*c* 1.2, CH_2Cl_2)}. Consequently, diastereoselectivity in the copper(I)-catalyzed cyclization of menthyl ester **7b** is dependent on the catalyst stereochemistry and relatively independent of the menthyl group.

The reactions described in this paper are the first enantioselective copper-catalyzed C–H insertions of α-diazo carbonyl compounds. While the optical yields for these processes are not high, we have found chloroform to be a superior solvent and are currently screening other chiral nitrogen ligands as well as sources of copper(I) in order to obtain enhanced enantioselectivities. Finally, we are applying this strategy to the synthesis of the antitumor agent FR-900482 and other nitrogen heterocycles.

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Supplementary Material Available: Experimental procedures and spectral data for all compounds (11 pages).

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(10) (a) We have observed variation in the enantio- and diastereoselectivity of the C–H insertion reactions. For example, on the three occasions we have employed Cu(I)·**3a** in the decomposition of diazo ester **7a**. Subsequent oxidation of the anti isomer **8** afforded **10** in 48, 44, and 40% ee. This observation suggests that there may be more than one active catalyst present. (b) The presence or absence of molecular sieves has no effect on the sense of asymmetric induction.

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