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α-HYDROXY ESTERS AS INEXPENSIVE CHIRAL AUXILIARIES IN RHODIUM(II)-CATALYZED CYCLOPROPANATIONS WITH VINYLDIAZOMETHANES

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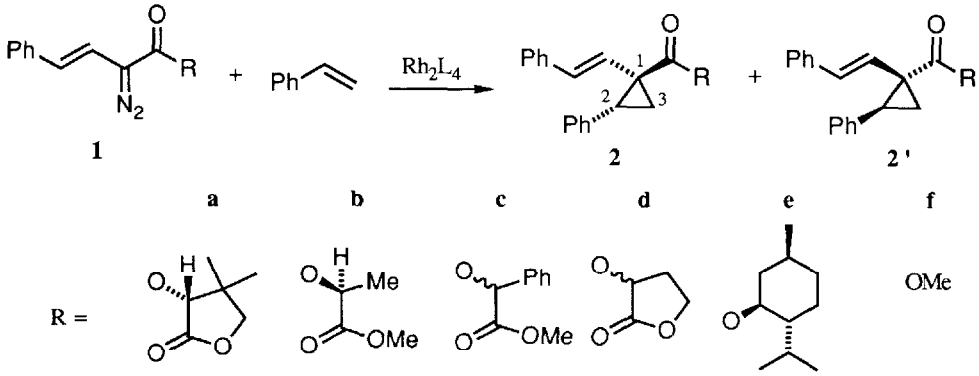
Summary: High levels of asymmetric induction were achieved in rhodium(II) catalyzed cyclopropanations with chiral vinyldiazomethanes. (R)-(-)-Pantolactone is the most effective chiral auxiliary, but other α-hydroxy esters also give reasonable levels of diastereoselectivity.

In recent years, great strides have been made in metal catalyzed asymmetric cyclopropanations of α-ketocarbenoids with the development of several highly effective chiral copper[1] and rhodium[2] catalysts. Even though remarkable levels of enantioselectivity are now possible, one drawback of alkyl diazoacetate cyclopropanations is that mixtures of cis and trans isomers are produced.[3] In contrast, we have found that vinyldiazomethanes undergo remarkably stereoselective cyclopropanations.[4] Vinyldiazomethanes, however, are prone to rearrangement to 3*H*-pyrazoles,[5] and this would be incompatible with the long reaction times or high temperatures required in the copper catalyzed cyclopropanations. Doyle's remarkable rhodium catalysts[2a,b] were not available at the outset of this work, and only modest enantioselectivity would have been anticipated with the other known rhodium catalysts.[2c,d] Consequently, chiral auxiliaries on the vinylcarbenoid appeared to be the most viable strategy to achieve asymmetric induction, but in order to compete with the chiral catalyst technology, these auxiliaries would need to be highly effective and inexpensive.

The previously used chiral carbenoid auxiliaries have either been ineffective,[6] at least in the absence of a chiral catalyst,[1a-d] or have required a fairly elaborate synthesis.[7,8] Presumably, the main reason for the lack of success with carbenoid auxiliaries is that restriction of one face of the carbenoid by the auxiliary would be required, but this could easily lead to competing intramolecular side reactions. In searching for a suitable auxiliary, (R)-(-)-pantolactone[9] appeared to be a reasonable choice because it would be incapable of 5-membered ring formation by an intramolecular C-H insertion,[10] a very common side-reaction in carbenoid chemistry.

Vinyldiazomethane **1a** was readily prepared by a general procedure[4d] and upon rhodium(II) acetate catalyzed decomposition in the presence of 20 equivalents of styrene in refluxing dichloromethane, a remarkably clean transformation was observed (Scheme 1). A 91% yield of cyclopropanes was obtained which was readily shown by nOe analysis to consist of only the cis isomers **2a** and **2a'** (89% de). The formation of only cis products was consistent with our earlier work on vinylcarbenoid chemistry,[4] and the high yield demonstrated that the pantolactone auxiliary was not involved in side reactions to any significant extent.

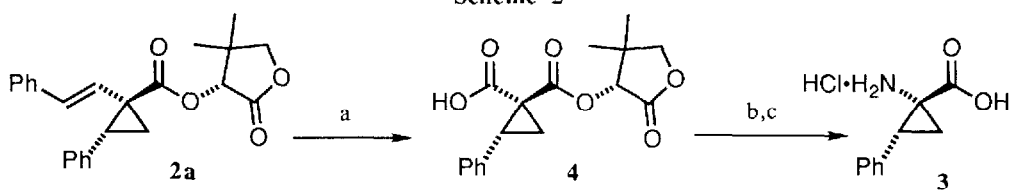
Scheme 1



Due to the success of this reaction, the effect of other catalysts was examined, and the results are summarized in the Table (entries 1-8). The trifluoroacetate and acetamide catalysts[3b] caused a drop in diastereoselectivity. In addition, the less reactive acetamide catalyst gave rise to a slower and more complicated reaction. Increasing the steric bulk of the catalyst, such as pivalate, caused a significant drop in diastereoselectivity. This was also seen in the mandelate series.[2c] Double stereodifferentiation between the chiral ligand and carbenoid auxiliary was clearly evident, but neither enantiomer of mandelate was as effective as the acetate catalyst. Improvement of the diastereoselectivity to 97% was possible by carrying out a reaction with rhodium(II) octanoate at 0 °C in dichloromethane. Diastereomerically pure material (>98% de, 63% yield) was readily obtained following a single recrystallization from isopropanol.

The absolute stereochemistry of the major product **2a** was determined by its conversion to the biologically interesting cyclopropylamino acid **3**[11] as shown in Scheme 2. Oxidative cleavage[12] of **2a** produced the acid **4** which was then converted to the cyclopropylamino acid **3** by means of a Curtius rearrangement (22% overall yield, $[\alpha]^{25}_D = +105°$ (c = .26, H_2O), lit[11] $[\alpha]^{25}_D = +105°$).[11,13]

Scheme 2



a: $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O; b: $(PhO)_2P(O)N_3$, NEt_3, toluene, reflux; c: 6M HCl, reflux.

The very high levels of asymmetric induction is indicative that a fairly rigid transition state must be involved. One way to limit conformational flexibility in this system is by an interaction of the carbenoid with the lactone carbonyl. In order to test this hypothesis, the reaction was repeated with a variety of α-hydroxy esters as auxiliaries and the results are summarized in the Table (entries 9-13). NMR analysis of the crude reaction mixtures revealed the levels of diastereoselectivity of **2b-e**. The absolute stereochemistry of **2b,b'** was related to **2a** by

Table. Rhodium(II) Catalyzed Asymmetric Cyclopropanation of Styrene by 1.

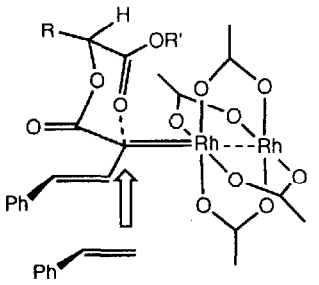
Entry	Substrate	Ligand	de,% (major isomer)	Yield, %
1	**1a**	O_2CCH_3	89 (1R, 2R)	91
2	**1a**	O_2CCF_3	78 (1R, 2R)	95
3	**1a**	$O(NH)CCH_3$	76 (1R, 2R)	37
4	**1a**	$O_2CC(CH_3)_3$	69 (1R, 2R)	95
5	**1a**	(S)-(+)-$O_2CCH(OH)(C_6H_5)$	17 (1R, 2R)	89
6	**1a**	(R)-(-)-$O_2CCH(OH)(C_6H_5)$	81 (1R, 2R)	95
7	**1a**	$O_2C(CH_2)_6CH_3$	87 (1R, 2R)	84
8	**1a**	$O_2C(CH_2)_6CH_3$	97 (1R, 2R)[a]	84[a]
9	**1b**	O_2CCH_3	67 (1S, 2S)	83
10	**1b**	$O_2CC(CH_3)_3$	67 (1S, 2S)	83
11	**1c**	O_2CCH_3	59 ([b])	71
12	**1c**	$O_2CC(CH_3)_3$	60([b])	81
13	**1d**	O_2CCH_3	42 ([b])	90
14	**1e**	O_2CCH_3	3 ([c])	81

a: Reaction was carried out at 0 °C; b: The auxiliary was a racemic mixture; c: Absolute stereochemistry was not determined.

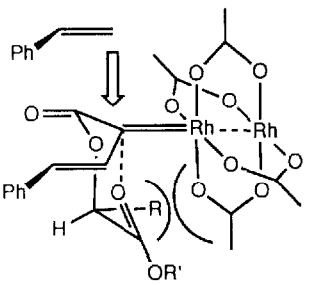
conversion of both to the methyl ester **2f**, followed by comparison of optical rotations. In the case of (S)-(-)-methyl lactate (**1b**) and (±)-methyl mandelate (**1c**), respectable levels of diastereoselectivity were observed. A drop in diastereoselectivity was observed with (±)-5-hydroxybutyrolactone (**1d**), which demonstrated that the *gem*-dimethyl fuctionlity in (-)-pantolactone (**1a**) has an important role. When (+)-menthol (**1e**) was used as an auxiliary (entry 14), a very low level of diastereoselectivity was observed. Based on these results, it would appear that a suitably disposed carbonyl functionality is critical for achieving high levels of asymmetric induction in these reactions.

A reasonable transition state to explain these results is shown in Figure 1.[14] The key element of this model is an interaction between the carbene and the carbonyl of the auxiliary, but the extent of this interaction is not enough

Figure 1



Conformer A



Conformer B

to inhibit carbenoid reactivity and lead instead to ylide chemistry.[15] This type of interaction has been proposed earlier by Doyle[6] as a possible mechanism for achieving high asymmetric induction in carbenoid reactions, but the chiral amide auxiliaries that he used were largely unsuccessful. Doyle has also proposed[2a,b] that interaction between a carbenoid and an ester funtionality on the ligand was a crucial factor for high enantioselectivity with the new chiral rhodium catalysts that he has developed.

The stereochemical results observed here are consistent with cyclopropanation through conformer A. Presumably conformer B is disfavored because the bulky group (R) would point towards the metal complex. In the case of pantolactone, it would appear that the interaction between the carbenoid and the carbonyl decreased as the ligands became more bulky, although this trend was not observed with methyl lactate and methyl mandelate.

In summary, high levels of diastereoselectivity are possible in cyclopropanations with vinyldiazomethanes using inexpensive α-hydroxyesters as chiral auxiliaries. Interaction of the ester carbonyl of the auxiliary with the carbenoid appears to be a critical element to obtain a rigid transition state for high asymmetric induction. The great advantage of using vinyldiazomethanes over alkyl diazoacetates is that E/Z mixtures of cyclopropanes are avoided.

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