Pergamon

Tetrahedron Letters, Vol. 38, No. 34, pp. 5955-5958, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01353-1

Enantioselective Intermolecular Free Radical Conjugate Additions. Application of a Pyrazole Template

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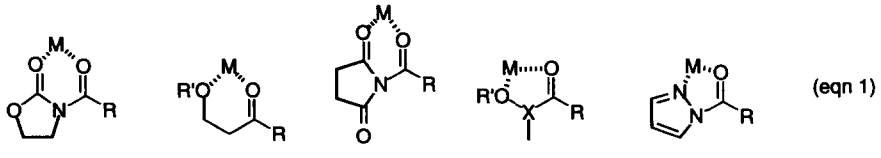
Abstract: An achiral pyrazole template has been evaluated in enantioselective conjugate radical additions. The enantioselectivity using the pyrazole template is inferior to those obtained from an oxazolidinone template. The two templates give products of opposite configuration using the same chiral Lewis acid. © 1997 Elsevier Science Ltd.

The choice of the achiral template for chiral Lewis acid-mediated enantioselective reactions is very important. It is an integral part of the substrate-Lewis acid complex which must be ordered to provide face shielding (see eqn 1 for a select group of templates). Oxazolidinones **1** are amongst the most widely used achiral templates for the evaluation of enantioselective transformations[1] such as Diels-Alder reactions,[2] dipolar cycloadditions,[3] and free radical ρ-allylations.[4] We have recently reported the first examples of chiral Lewis acid-mediated conjugate radical additions using an oxazolidinone template.[5,6] In these reactions, the template forms a six-membered chelate with the chiral Lewis acid.[7] We have been interested in exploring alternative achiral templates wherein the substrate has the potential for the formation of a five-membered chelate with the chiral Lewis acid.[8] Functionalized pyrazoles have been shown to be useful chiral auxiliaries by Kashima and co-workers in several different transformations.[9] The use of pyrazoles **5** as the achiral platform in enantioselective conjugate radical addition was the subject of this investigation.

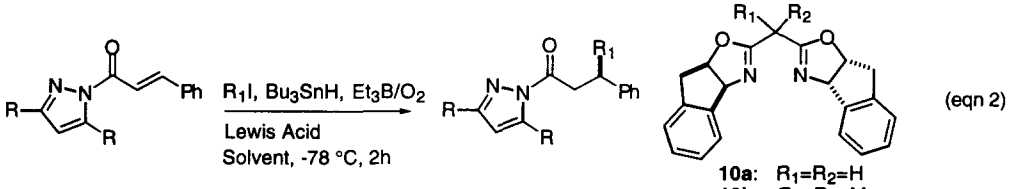


1 **2** **3** **4** X = CH_2, N **5** M = Metal

The addition of the nucleophilic isopropyl radical to the *N*-cinnamoyl pyrazole **6** under a variety of reaction conditions was examined initially (eqn 2). Reactions with **6** were inefficient even in the presence of Lewis acids[10] [no Lewis acid <10%; $MgBr_2$ 27%; $Yb(OTf)_3$ 52%] and thus evaluation of chiral Lewis acids was not carried out.

The cinnamate **7** derived from 3,5-dimethylpyrazole[11] underwent radical addition with variable efficiency depending on the Lewis acid [no Lewis acid <10%; MgI_2 30%; $Mg(OTf)_2$ <10%; $ZnBr_2$ 70%; $Zn(OTf)_2$ 50%; $Yb(OTf)_3$ 50%; ZnI_2 50%]. The next series of experiments were designed to explore the

effect of chiral Lewis acids on conjugate additions. The complexes prepared from **10d**[12,13] and several Lewis acids were screened [for isopropyl radical addition: MgI_2 60% (9%ee); $ZnBr_2$ <20%; $Zn(OTf)_2$ 76% (51%ee); ZnI_2 <20%]. Of these, zinc triflate gave consistently better results with regards to both chemical as well as stereochemical efficiency. The higher chemical yields using zinc triflate-ligand is most likely due to its complete solubility in CH_2Cl_2 as compared to $Zn(OTf)_2$ alone which is sparingly soluble.

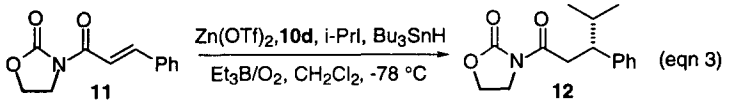


6 R =H
7 R = CH_3

8 R =H, R_1 = i-Pr
9a R = CH_3; R_1 = i-Pr
9b R = CH_3; R_1 = Et
9c R = CH_3; R_1 = Cyclohexyl

10a: R_1=R_2=H
10b: R_1=R_2=Me
10c: R_1=R_2=$PhCH_2$
10d: R_1, R_2=CH_2CH_2
10e: R_1, R_2=$CH_2CH_2CH_2$
10f: R_1, R_2=$CH_2CH_2CH_2CH_2$

Results from the $Zn(OTf)_2$ mediated conjugate additions are presented in the Table.[14,15] Several interesting trends can be discerned from the table. The chemical yields with the pyrazole template is good,[16] however, the levels of enantioselectivity for **9a** is moderate at best. The highest level of enantioselectivity with the pyrazole template using stoichiometric chiral Lewis acid for **9a** is ~50% (entries 1-6). Enantioselectivity for **9a** decreases when substoichiometric amounts of the Lewis acids are used in the reaction (compare entry 3 with 7 and 4 with 8). The configuration of **9a** was determined to be *S* by hydrolysis to the corresponding acid{for entry 4: $[\alpha]_D^{25}$ = -19.36 (c=0.31, $CHCl_3$); lit. data for (*S*) isomer: $[\alpha]_D^{25}$ = -34.44 (c=4.06, $CHCl_3$}.[17] In contrast, isopropyl radical addition to *N*-cinnamoyl-2-oxazolidinone **11** using ligand **10d** and $Zn(OTf)_2$ gave a conjugate addition product **12** with *R* configuration in 84% chemical yield and 51% ee (eqn 3).[18] Thus, the pyrazole and oxazolidinone templates give products of opposite configuration using the same chiral Lewis acid.



11 **12**

The addition of other nucleophilic radicals to **7** was also examined. Ethyl radical addition to **7** under the optimal conditions gave **9b** in good chemical yield and moderate enantioselectivity (entry 9) [*R* configuration for the product represents the same sense of radical addition as for **9a**]. Slightly higher levels of enantioselectivity were obtained for cyclohexyl radical addition[16] to **7** (entries 10-14) with **10d** providing for the best result (81% ee, entry 11).

A working hypothesis for the observed selectivity with pyrazole template is as follows. NMR experiments from Kashima's laboratory indicate that simple *N*-acyl pyrazoles form a chelate with magnesium bromide.[19] The product configuration is consistent with radical addition to the *si* face of the *s-cis* rotamer of **7**, which may react via a square planar (structure **A**) or *trans* octahedral (structure **B**) zinc complex.[13] The reasons for the different stereochemical outcome with the pyrazole and oxazolidinone templates are unclear at the present time. In summary, we have shown that conjugate radical additions to enoates derived from

pyrazoles show moderate enantioselectivity but interesting stereochemical outcome. Experiments to understand the product stereochemistry and examination of other achiral templates capable of forming five-membered chelates are underway.

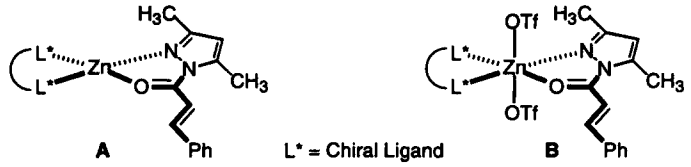


Table. Enantioselective Radical Addition to *N*-Cinnamoyl-3,5-Dimethylpyrazole 7 Using $Zn(OTf)_2$[a]

Entry	R	Ligand (eq)	Product	Yield (%)[b]	ee (%)[c] (Configuration)[d]
1	i-Pr	**10a** (1.0)	**9a**	83	40 (S)
2	i-Pr	**10b** (1.0)	**9a**	72	43 (S)
3	i-Pr	**10c** (1.0)	**9a**	88	44 (S)
4	i-Pr	**10d** (1.0)	**9a**	76	51 (S)
5	i-Pr	**10e** (1.0)	**9a**	81	44 (S)
6	i-Pr	**10f** (1.0)	**9a**	90	50 (S)
7	i-Pr	**10c** (0.3)	**9a**	67	21 (S)
8	i-Pr	**10d** (0.3)	**9a**	84	39 (S)
9	Et	**10d** (1.0)	**9b**	80	39 (R)
10	cyclohexyl	**10b** (1.0)	**9c**	88	43[e]
11	cyclohexyl	**10d** (1.0)	**9c**	81	81[e]
12	cyclohexyl	**10e** (1.0)	**9c**	85	33[e]
13	cyclohexyl	**10f** (1.0)	**9c**	93	51[e]
14	cyclohexyl	**10d** (0.3)	**9c**	76	39[e]

[a] To chiral Lewis acid (0.1 mmol), **7** (0.1 mmol), i-PrI (0.5 mmol), Bu_3SnH (0.2 mmol, Et_3B (0.2 mmol) in CH_2Cl_2 (2 mL) at -78 °C was added oxygen through a syringe. After completion (TLC) and normal work up the product was isolated by chromatography. [b] Yields are for isolated and column purified materials. [c] The ees were determined by chiral HPLC (Chiralcel OJ column) analysis. [d] The configuration of **9a** and **9b** was established by lithium hydroperoxide hydrolysis and comparison of the product acid's sign of rotation with those reported in the literature.[20] [e] The configuration of **9c** is unknown.

Acknowledgment: Financial support for this program was provided by NIH (GM-54696).

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(*Received in USA* 13 *June* 1997; *revised* 26 *June* 1997; *accepted* 27 *June* 1997)