Pergamon

Tetrahedron Letters 40 (1999) 6713–6716

TETRAHEDRON
LETTERS

Enantioselective reactions of radicals at the α position of γ-lactams

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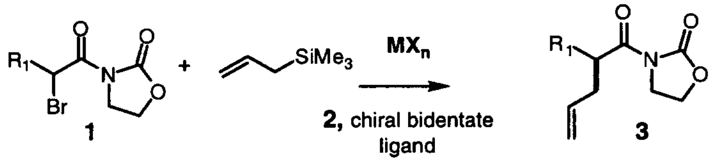
Received 8 June 1999; accepted 7 July 1999

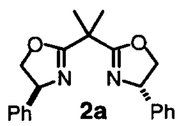
Abstract

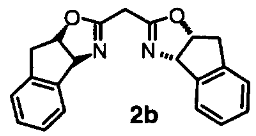
γ-Lactams derived from 2-aminopyridines undergo free radical reactions with allyltrimethylsilane in the presence of Lewis acids and chiral bisoxazolines. Products have been obtained with enantiomeric excesses as high as 99%. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: radicals; radical reactions; addition reactions; enantioselection; oxazolidinones; Lewis acids; γ-lactams.

The control of stereochemistry in free radical reactions has received increased attention in the past several years.[1] Success in this endeavor has been achieved in the reactions of radicals substituted α to oxazolidinones that are complexed with chiral Lewis acids, MX_n. In a typical transformation, the α bromo compound **1** is reacted with allyltributylstannane or allyltrimethylsilane in the presence of Lewis acids such as $Zn(OTf)_2$ and a chiral bidentate ligand **2** to give the allyl transfer product **3**.[2] For the system in which R_1=^{t}Bu-CH_2 enantioselectivities as high as 94% may be achieved in the conversion of **1** to **3**.




2a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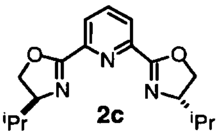
2c

In an effort to explore radicals having differing basicities in Lewis acid promoted free radical reactions, we have examined a series of substituted lactam radicals, **4**, generated from substituted 2-aminopyridines.

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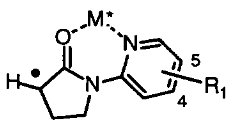
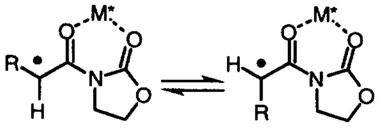
PII: S0040-4039(99)01370-2

Radicals derived from **4** permit the modification of the Lewis base in a rational way by variation of the substituent R_1. It is also noteworthy that the lactam-derived radical has a fixed orientation of groups on the radical. By comparison, the radical **5** derived from **1** has two conformations that are possible for the chelated radical species. One conformer has the *Z* arrangement about the carbonyl α carbon bond; the other has an *E* orientation about this rotatable bond. While the **5**-*Z* conformer is preferred in simple α amide radicals, it is not clear that this is also the case if such radicals are complexed to sterically crowded Lewis acids. The radical **4**, having one nitrogen ligand and the radical constrained in a ring, would appear to be a better Lewis base than **5**-*Z*.

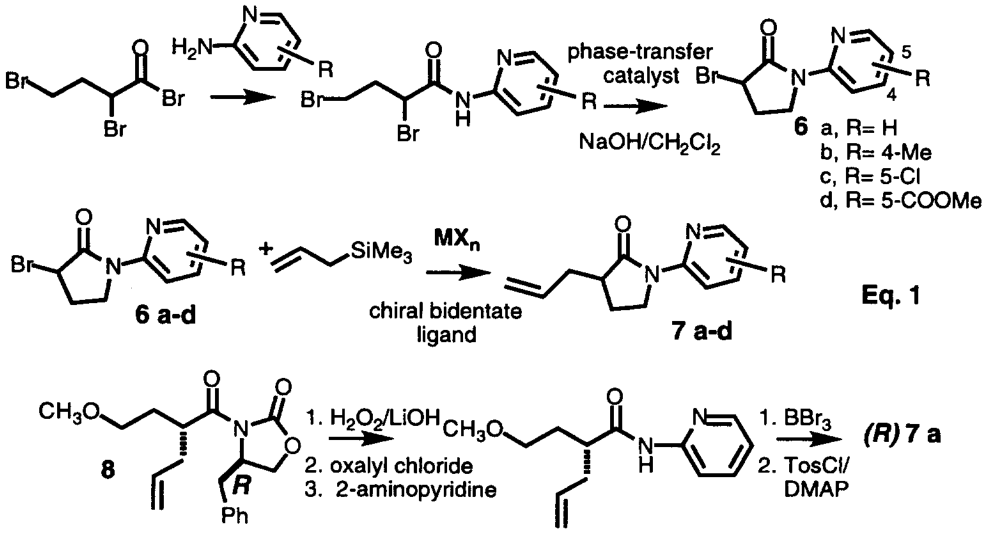


4



5-*Z* **5-*E***

The radical precursors **6a–d** were prepared in two steps from known precursors as shown in Scheme 1. Yields for the first step, reaction of 2,4-dibromobutyryl bromide[3] with the aminopyridine were good to moderate, 65–85%, as were those for the conversion of the amides to the lactams, 60–95%.[4] The bromolactams, **6a–d** reacted with allyltrimethylsilane in reactions initiated by triethylborane in the presence of Lewis acids.[5] The products **7a–d** were purified by chromatography and successfully analyzed by enantioselective GC, which separated the enantiomers for each of the products. The *R* enantiomer of **7a** was prepared by independent synthesis as outlined in Scheme 1. Briefly, the methoxy compound **8**, prepared by free radical addition chemistry[6,7] was converted to the primary amide, demethylated with BBr_3, and the product alcohol cyclized with tosyl chloride and DMAP (84% enantiomeric excess carried through from the benzyl oxazolidinone).



Scheme 1.

Several Lewis acids, including $MgBr_2$, MgI_2, $Zn(OTf)_2$, $Cu(OTf)_2$, and $Yb(OTf)_3$ were used in conjunction with chiral ligands including **2a–c** to promote the conversion of **6a–d** to **7a–d**. Reactions were carried out over a range of temperatures and with varying amounts of Lewis acid and chiral ligand present in the reaction mixture. The results of some representative conversions are shown in Table 1. Yields are generally modest to excellent. In some cases, a product in which ethyl replaces the bromide of

Table 1

Lewis acid promoted free radical reactions of **6a–d**, Eq. 1

Entry	Reactant	Ligand	Lewis Acid, (eq.)	T, °C	Yield, %	ee of 7 (*R/S*)
1	6a	2a	$Zn(OTf)_2$ (1.0)	-78	70	59 (*S*)
2	6a	2b	$Zn(OTf)_2$ (1.0)	-78	75	96 (*S*)
3	6a	2c	$Zn(OTf)_2$ (1.0)	-78	42	75 (*S*)
4	6a	2b	$MgBr_2$ (1.0)	-78	54	84 (*S*)
5	6a	2b	$Zn(OTf)_2$ (2.0)	-78	83	>99 (*S*)
6	6a	2b	$Zn(OTf)_2$ (2.0)	-20	94	95 (*S*)
7	6a	2b	$Zn(OTf)_2$ (1.0)	-20	93	91 (*S*)
8	6b	2b	$Zn(OTf)_2$ (1.0)	-20	85	70 (*S*)
9	6c	2b	$Zn(OTf)_2$ (1.0)	-20	88	67 (*S*)
10	6d	2b	$Zn(OTf)_2$ (1.0)	-20	91	80 (*S*)
11	6a	2b	$Zn(OTf)_2$ (0.2)	-20	69	81 (*S*)

6 is observed although this compound never comprises over a few percent of the product mixture. This compound derives from triethylborane, which is used as an initiator.

It is noteworthy that bisoxazoline **2b**-$Zn(OTf)_2$ proves to be the most effective chiral ligand-Lewis acid pair that we have investigated in this transformation, giving enantiomeric excesses above 99% at –78°C when present in a twofold excess (entry 5) and good results at –20°C with only 20% of Lewis acid and ligand present (entry 11). In analogous reactions of acyclic precursors such as **1**, products formed with this chiral agent **2b** and $Zn(OTf)_2$ are racemic.[7] Indeed, the most effective chiral ligand in the transformations of **1** is ligand **2a**,[8] which performs only modestly in the reactions of **6**. Of further note is the fact that reactions of the lactam radical **4** promoted by either zinc or magnesium salts give the same major enantiomer when ligands **2b** and **2c** are used. The combination of **4** and **2a**, on the other hand, gives opposite enantiomers depending on whether zinc or magnesium Lewis acids are used. Substituents on the pyridine ligand in the 4 and 5 positions, entries 7–10, appear to affect the selectivity of the transformation but the effect does not reflect the Lewis basicity of the ligand in any straightforward way.

The configuration of the product formed in reactions of radical **4** and ligand **2b** is consistent with a *trans* octahedral model,[1a] with the triflates *trans* and the chiral ligand and radical complexed in the same plane, Fig. 1. With acyclic radicals such as **5**, this crowded complex with **2b** apparently does not form. This may be due to steric crowding caused by *R* in conformation **5**-*Z* as well as the fact that oxazolidinone-derived **5** is presumably less Lewis basic than the pyridine-derived **4**. In this regard, we note that reactions of radical **4** proceed with significant enantioselectivity in THF (75% ee) and acetonitrile (67% ee) with one equivalent of zinc triflate and ligand **2b** at –20°C. Reactions proceeding through **5** give racemic products in these solvents under all conditions.

The *trans* octahedral model proposed for reactions of radical **4** is analogous to the model proposed for addition of isopropyl radical to the complexed cinnamate **9** in reactions promoted by $Zn(OTf)_2$ and ligand **2b**.[9] A common model accounts for reactions of complexes acting as a radical trap, i.e. **9**, or as a radical i.e. **4** in these closely related systems.

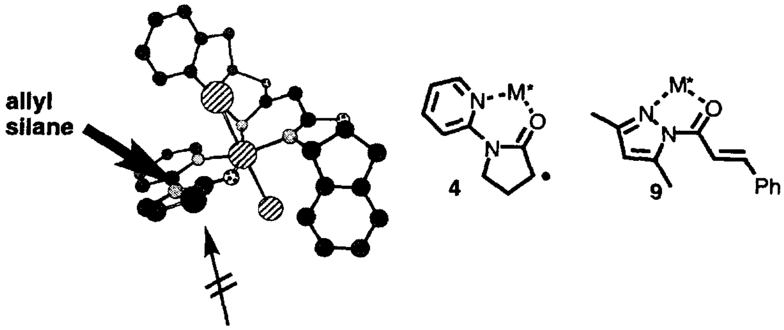


Figure 1. Octahedral complex model of **4** with ligand **2b** and Zn(OTf)$_2$

Acknowledgements

Support for this research by the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

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8. Ref. 2a, see also: Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029–11030.
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