Enantioselective Tandem Radical Reactions: Vicinal Difunctionalization in Acyclic Systems with Control over Relative and Absolute Stereochemistry

Mukund P. Sibi* and Jianxie Chen

Department of Chemistry
North Dakota State University
Fargo, North Dakota 58105-5516

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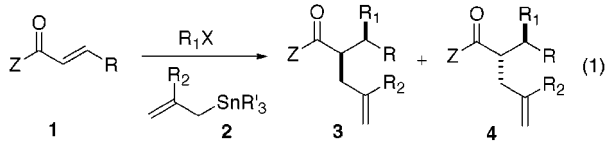
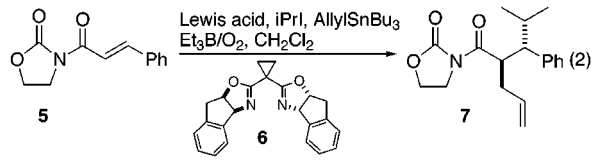
Following addition of a radical to an alkene, the adduct radical can be trapped by a variety of reagents, for example, allyl stannane, CO, C═C, C═X, and so forth, providing convenient protocols for the formation of multiple C−C bonds.[1] Tandem addition−trapping reactions of this type are attractive for the establishment of two C−C bonds in a single operation. Both the addition and trapping steps can be either intra- or intermolecular, and tandem intra- and intermolecular radical reactions have been sequenced in a variety of creative and useful ways.[2] Enantioselective radical reactions[3] where stereochemistry has been established either α[4] or β[5] to a carbonyl group have been reported. However, at present there are no examples of tandem intermolecular addition-intermolecular trapping reactions involving acyclic systems where chirality is established at both β- and α-centers with control over both absolute and relative stereochemistry.[6] This work reports the first examples where two C−C bonds are formed (eq 1) with high stereocontrol by nucleophilic radical addition to an enoate **1** followed by trapping with allyl stannane **2**. Additionally, factors which influence 1,2-diastereoselectivity[7] in these systems are also described.



Our work began with the addition of nucleophilic isopropyl radical to cinnamate **5** and trapping of the intermediate radical with allylstannane using a chiral Lewis acid (eq 2, Table 1). We have previously established that bisoxazoline **6** with Mg(II) and Zn(II) salts are very competent chiral Lewis acids for conjugate radical additions.[5] Addition/trapping reaction with **5** using a stoichiometric amount of MgI_2/**6** at −78 °C gave **7** in excellent yield and high diastereo- and enantioselectivity (entry 1). The relative stereochemistry for the product **7** was established as anti (vide infra). Reducing the catalyst loading to 30 mol % led to improvement in selectivity as well as yield (entry 2). *Thus, two contiguous chiral centers could be established in a single operation with excellent selectivity.* Increasing the reaction temperature had a deleterious effect on both yield and selectivity (entry 3). $MgBr_2$ and $Mg(ClO_4)_2$ gave similar results (entries 4 and 5) using allyltributyltin and substoichiometric amount of the catalyst. Zinc triflate was also effective in these reactions (entry 6). Copper Lewis acids which are generally unsuccessful under reductive conditions were quite efficient in addition trapping experiments (entries 7 and 8). However, these reactions required the use of allyltriphenyltin.[8] *The most noteworthy outcome of these experiments was that Mg and Cu Lewis acids gave enantiomeric products using the same chiral source.*[9]

Table 1. Optimization of Reaction Conditions for Addition-trapping Experiments



entry	Lewis acid (equiv)	temp °C	yield (%)[a]	dr[b]	ee (%)[c]
1	MgI_2 (1)	−78	82	19:1	86
2	MgI_2 (0.3)	−78	93	37:1	93[d]
3	MgI_2 (0.3)	−40	70	36:1	65
4	$MgBr_2$ (0.3)	−78	90	30:1	90
5	$Mg(ClO_4)_2$ (0.3)	−78	91	40:1	87
6	$Zn(OTf)_2$ (0.3)	−78	69	33:1	−43
7	$Cu(OTf)_2$ (1)	−78	84[e]	30:1	−76
8	$Cu(OTf)_2$ (0.3)	−78	93[e]	30:1	−79

[a] Isolated yield. [b] Determined by NMR and HPLC. [c] Determined by HPLC. [d] Reaction using allyltriphenyltin gave **7** in 82% yield (36:1 dr and 91% ee). [e] Allyltriphenyltin was used.

In an effort to understand the origin for the high diastereo- and enantioselectivity in these addition/trapping experiments, the size of the radical and the β-substituent on the acceptor was varied (eq 3, Table 2). As can be discerned from the table, a variety of radicals add efficiently to the cinnamate **5** (entries 1−5). The stereoselectivity has a linear correlation with the effective size of the nucleophilic radical: the larger the radical the higher the stereoselectivity.[10] *Reaction with t-BuI using MgI_2 as a Lewis acid was highly selective providing **10** with 99:1 diastereoselectivity*

(1) (a) For general aspects of tandem reactions see the whole issue of *Chem. Rev.* **1996**, *96*, issue 1. (b) Specifically see: Tietze, L. F. *Chem. Rev.* **1996**, *96*, *115*. (c) For radical reactions see: Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH, Weinheim, 2001

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(6) Enantioselective tandem C−C bond formation using ionic intermediates. (a) Yamada, K−i.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666. (b) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104. (c) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104. (d) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; deVries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (e) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358. (f) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841.

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(8) Allyltriphenyltin has been occasionally used as allylating agent in radical reactions and may have improved reactivity. (a) Curran, D. P.; van Elburg, P. A.; Giese, B.; Gilges, S. *Tetrahedron Lett.* **1990**, *31*, 2861. (b) Clive, D. L. J.; Paul, C. C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028.

(9) For a review on reversal of stereochemistry see: (a) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719. (b) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (c) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

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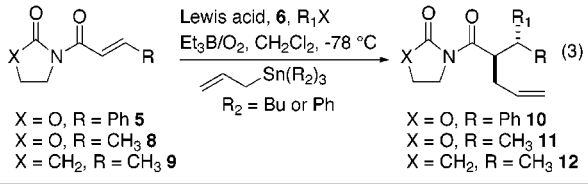
Table 2. Conjugate Addition of Different Radicals



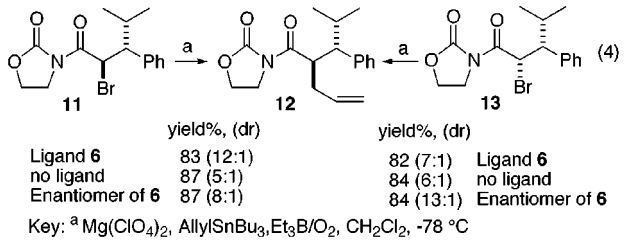
entry	sub.	R_1X	LA (0.3equiv)	yield (%)[a]	dr[b]	ee (%)[c]
1	**5**	$MeOCH_2Br$	MgI_2	80	20:1	72
2	**5**	EtI	MgI_2	79	32:1	77
3	**5**	c-HexI	MgI_2	80	60:1	92
4	**5**	*i*-PrI	MgI_2	93	37:1	93
5	**5**	*t*-BuI	MgI_2	84	99:1	97
6	**5**	*i*-PrI	$Cu(OTf)_2$	93[d]	30:1	−79
7	**5**	*t*-BuI	$Cu(OTf)_2$	90[d]	99:1	−96
8	**8**	EtI	$Mg(ClO_4)_2$	83	4:1	61
9	**8**	c-HexI	$Mg(ClO_4)_2$	83	4:1	62
10	**9**	EtI	$Mg(ClO_4)_2$	83	7:1	66
11	**9**	c-HexI	$Mg(ClO_4)_2$	84	7:1	69
12	**9**	$MeOCH_2Br$	$Mg(ClO_4)_2$	83	2.4:1	53
13	**9**	*i*-PrI	$Mg(ClO_4)_2$	84	7:1	76
14	**9**	*i*-PrI	$Cu(OTf)_2$	95[d]	10:1	−76
15	**9**	*t*-BuI	$Mg(ClO_4)_2$	85	19:1	92
16	**9**	*t*-BuI	$Cu(OTf)_2$	66[d]	50:1	−83

[a] Isolated yield. [b] Determined by NMR and HPLC. [c] Determined by HPLC. [d] Allyltriphenyltin was used.

and 97% ee (entry 5). Alternatively, Cu(OTf)$_2$ as the Lewis acid gave the enantiomeric product with similar levels of selectivity (entry 7). The structure for the *tert*-butyl radical addition product (**10**, R = Ph, R_1 = *t*-Bu) was confirmed by X-ray crystallography.[11] This clearly establishes that the addition and trapping occurs in an anti manner.

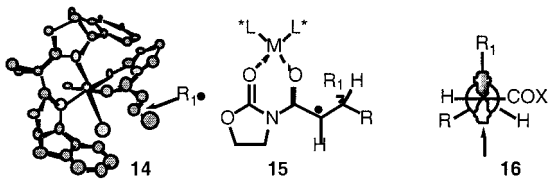
Experiments with oxazolidinone (**8**) and pyrrolidinone (**9**) derived crotonates were equally effective (entries 8−11). The stereoselectivity in the crotonate series were lower than those with the cinnamate (compare entry 2 with 8 and 3 with 9). The diminished selectivity with the crotonate is a consequence of the smaller β-methyl substituent on the acceptor. Increasing the size of the radical led to higher selectivity (compare entries 10, 13 and 15) for reactions with **9** with the *tert*-butyl radical providing the highest diastereo- as well as enantioselectivity (entry 15). These results parallel those observed with the cinnamates. Reactions with Cu(OTf)$_2$ as the Lewis acid again gave enantiomeric products in comparison to reactions with Mg(II) salts (compare entry 13 with 14 and 15 with 16). The anti stereochemistry for **12** (R = Me and R_1 = *t*-Bu) was established by converting it to a known compound.[12] *The data in Table 2 clearly demonstrates the versatility of the tandem addition/trapping strategy for establishing contiguous chiral centers in acyclic systems with high selectivity for a variety of substrates.*

To probe whether the formation of stereochemistry at the α-center in the trapping step is primarily determined by the ligand or the β-center, substrates **11** and **13** were prepared in enantiomerically pure form (equation 4).[11] Allylation of **11** or **13** using $Mg(ClO_4)_2$ as a Lewis acid gave **12** in a ∼5:1 ratio. When Mg-$(ClO_4)_2$-ligand **6** was used, the selectivity increased to 12:1. When the enantiomer of ligand **6** was used, the selectivity was 8:1. Similar observations were made with the syn diastereomer **13**. These results suggest that the stereochemistry at the β- carbon is the primary determinant of α- stereochemistry, although there is some matching/mismatching by the ligand.



We have previously proposed a working model for the stereochemistry observed in the conjugate addition of radicals to enoates using a chiral Lewis acid derived from Mg(II) compounds and ligand **6**. Addition of radicals to the enoate as indicated in **14** provides the intermediate radical ready for trapping. Enantioselectivity in the addition step increases when either the radial (entries 1−5, Table 2) or the R group (Ph vs Me) increases in size. The formation of enantiomeric product with copper Lewis acid suggests an alternate geometry for the ternary complex and product stereochemistry is consistent with a square planar arrangement.[9]

Following addition, trapping occurs in an anti manner, whether Mg or Cu Lewis acid is used, and regardless of whether R_1 is larger or smaller than R. The adduct radical is initially formed in the conformation **15** where the R_1 blocks syn allylation. Modest rotation could produce conformation **16**, which would also result in anti allylation. It is interesting to note that tandem addition (37:1, entry 2, Table 1) occurs with much higher selectivity than allylation of the bromides **11** and **13** (12:1, eq 4). The difference suggests that full rotameric equilibration does not occur in the tandem process and that the chiral Lewis acid is coordinated continuously (chelation) in the tandem process but not in the allylation[13] of the less basic bromides **11** and **13**. Trapping via **15** or **16** is consistent with higher diastereoselectivity where R_1 is relatively large (99:1 with *t*-Bu, 32:1 with Et, entries 5 and 2) or when R is relatively large [40:1 with Ph (entry 5, Table 1), 19:1 with Me (entry 15, Table 2)]. Experiments are underway to further refine our model and extend the tandem process to more complex systems.



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Supporting Information Available: Characterization data for compounds **3**−**13** and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See Supporting Information for details.

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