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Highly cis- and trans-selective alkyl radical addition to α-methylene-γ-phenyl-γ-butyrolactams

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ABSTRACT

The 1,3-asymmetric induction in alkyl radical additions to α-methylene-γ-phenyl-γ-butyrolactams was investigated. The reactions of N-unsubstituted lactam using $(Me_3Si)_3SiH$ under UV irradiation give *cis*-α,γ-disubstituted lactams, whereas reactions of *N*-pivaloyllactams using Et_3B and Bu_3SnH in the presence of $Yb(OTf)_3$ give *trans*-α,γ-disubstituted lactams, both with high diastereoselectivities.

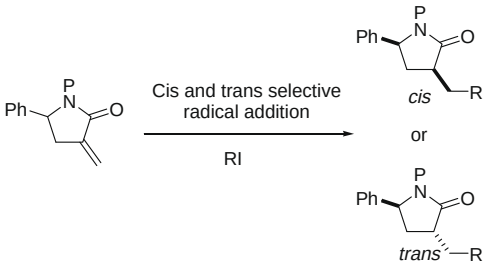
Stereocontrol in radical-mediated carbon–carbon bond-forming reactions has been investigated with great interest, and significant levels of diastereoselectivity have been well documented in reactions involving a stereogenic center adjacent to the radical center (1,2-asymmetric induction).[1] However, there are a limited number of reports on radical-mediated 1,3-asymmetric induction.[2–4] Moreover, most of them are concerned with the preparation of one diastereomer, and only a few reports are known to provide either diastereomer efficiently.[5] Herein, we report that 1,3-asymmetrically induced alkyl radical additions to α-methylene-γ-phenyl-γ-butyrolactams provided both cis- and trans-products successfully, simply by changing the combination of the N-protecting groups of the starting lactams and the radical reaction conditions (Scheme 1).

Our investigation began with the radical reaction of α-methylene-γ-phenyl-γ-butyrolactam (**1**)[6] with *i*-PrI in CH_2Cl_2 (Table 1). The radical addition to lactam **1** using Et_3B and *n*-Bu_3SnH afforded adduct **4** with cis-stereoselectivity (entry 1). Entry 2 shows that the addition of $MgBr_2$-OEt_2 improved the yield of **4**, although the diastereoselectivity remained unchanged. For improving cis-selectivity, *n*-Bu_3SnH was replaced by $(Me_3Si)_3SiH$ (TTMSS) as a H radical donor.[7] The reaction of **1** under UV irradiation in the presence of TTMSS and 2,2′-azobis(isobutyronitrile) (AIBN) gave adduct **4** with higher cis-selectivity (entry 3). The radical reaction of *N*-(*t*-butoxycarbonyl)lactam **2** using Et_3B and *n*-Bu_3SnH in the absence of Lewis acid also proceeded to give **5** with cis-stereoselectivity (entry 4). However, the radical addition of *N*-(*t*-butoxycarbonyl)lactam **2** in the presence of $MgBr_2$–OEt_2 gave the Boc-eliminated product **4** with trans-selectivity (entry 5). The use of BF_3–OEt_2 also gave **4**, but with cis-selectivity (entry 6). To prevent the elimination of the N-substituent, *N*-pivaloyllactam **3** was used as a substrate. When lactam **3** was treated under the same conditions of entry 4, adduct **6** was obtained in 69% yield with cis-selectivity (entry 7). On the other hand, the reaction in the presence of $MgBr_2$-OEt_2 gave adduct **6** with high trans-selectivity (entry 8). Furthermore, the use of $Yb(OTf)_3$ improved both the yield and the stereoselectivity (entry 9).

Since the combinations of N-substituent and reaction conditions suitable for the diastereoselective additions were revealed, they were applied to the reactions with various alkyl iodides. The results are summarized in Table 2. Under the reaction conditions of entry 3 in Table 1 (conditions A), the cis-selectivities were over 92:8 for all alkyl iodides (entries 1–4). In contrast, the reactions using the conditions of entry 9 in Table 1 (conditions B) gave 24:76 to 14:86 trans-selectivities (entries 5–8).

Stereochemical outcome is determined at the stage of hydrogen radical transfer from *n*-Bu_3SnH or TTMSS to the intermediate radicals (Scheme 2). Under the conditions A, the hydrogen-atom transfer takes place predominantly from the less-hindered face of the radical center opposite to the face shielded by the γ-phenyl group.[7] The more sterically demanding character of TTMSS than *n*-Bu_3SnH could account for the higher selectivity. BF_3-OEt_2 coordinates the lactam monodentately, and does not affect the cis-selectivity.

In the case of the trans-selective reaction (conditions B), the coordination of the carbonyl oxygens to the metal reagent during



Scheme 1.

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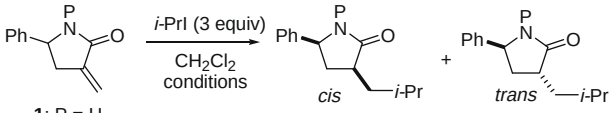
Table 1
Addition of *i*-PrI to α-methylene-γ-phenyl-γ-butyrolactams



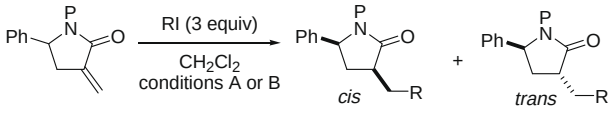
1: P = H
2: P = Boc
3: P = Piv

4: P = H
5: P = Boc
6: P = Piv

Entry	Substrate	Conditions	Product	Yield (%)	cis:trans[a]
1	**1**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), 0 °C	**4**	64	79:21
2	**1**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), $MgBr_2$–OEt_2 (3 equiv), 0 °C	**4**	92	77:23
3	**1**	$(Me_3Si)_3SiH$ (2 equiv), AIBN (0.2 equiv), *hv*, rt	**4**	55	93:7
4	**2**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), 0 °C	**5**	84	82:18
5	**2**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), $MgBr_2$–OEt_2 (3 equiv), 0 °C	**4**	70	18:82
6	**2**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), BF_3–OEt_2 (3 equiv), 0 °C	**4**	85	76:24
7	**3**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), 0 °C	**6**	69	68:32
8	**3**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), $MgBr_2$–OEt_2 (3 equiv), −78 °C	**6**	64	11:89
9	**3**	*n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), $Yb(OTf)_3$ (3 equiv), −78 °C	**6**	71	9:91

[a] Diastereomer ratios were determined by ^1H NMR. The relative configuration of **4** was assigned by NOE analysis. The relative configurations of **5** and **6** were determined by comparing the chemical shift values in ^1H and ^{13}C NMR with those of **4**.

Table 2
Addition of RI to α-methylene-γ-phenyl-γ-butyrolactams



1: P = H
3: P = Piv

7-10: P = H
11-14: P = Piv

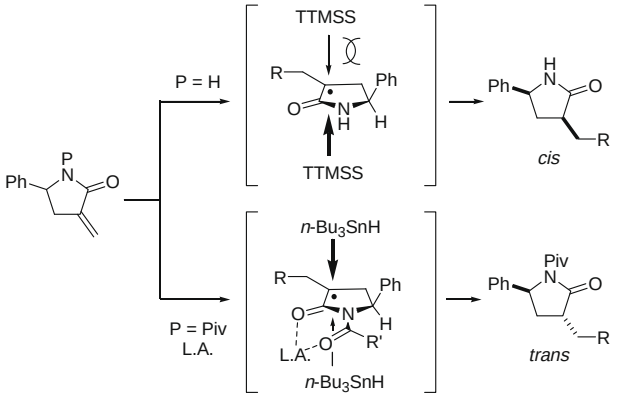
Entry	Substrate	Conditions [a]	R	Product	Yield (%)	cis:trans[b]
1	**1**	A	Et	**7**	75	98:2
2	**1**	A	*n*-Bu	**8**	55	93:7
3	**1**	A	*t*-Bu	**9**	62	94:6
4	**1**	A	Cyclo-hex	**10**	63	92:8
5	**3**	B	Et	**11**	75	14:86
6	**3**	B	*n*-Bu	**12**	94	20:80
7	**3**	B	*t*-Bu	**13**	66	20:80
8	**3**	B	Cyclo-hex	**14**	80	24:76

[a] Conditions A; TTMSS (2 equiv), AIBN (0.2 equiv), *hv*, rt. Conditions B; Bu_3SnH (2 equiv), Et_3B (1 equiv), $Yb(OTf)_3$ (3 equiv), −78 °C.

[b] Diastereomer ratios were determined by ^1H NMR. The relative configuration of **11** was assigned by NOE analysis. The relative configurations of **7**–**10** and **12**–**14** were determined by comparing the chemical shift values in ^1H and ^{13}C NMR with those of **4** and **11**, respectively.

the hydrogen transfer may participate in the face selectivity. The carbonyl oxygen of lactam and that of the N-protecting group (Boc or Piv) coordinate with the Lewis acid ($MgBr_2$–OEt_2 or $Yb(OTf)_3$) to form a six-membered chelate. The Lewis acid coordinates from the less-hindered convex face (opposite to the phenyl group), and forces the incoming hydrogen donor to attack the radical face where the phenyl is located.

In summary, we have reported that the 1,3-asymmetrically induced alkyl radical addition to α-methylene-γ-phenyl-γ-butyrolactams occurs with a remarkable diastereochemical switch. The reactions of lactam **1** using $(Me_3Si)_3SiH$ under UV irradiation give *cis*-α,γ-disubstituted lactams, whereas the reactions of *N*-pivaloyllactam **3** using Et_3B and *n*-Bu_3SnH in the presence of $Yb(OTf)_3$ give trans-disubstituted lactams. Because synthetic methods for such α,γ-disubstituted lactams are scarce, this methodology provides an efficient stereoselective synthetic route to new lactam compounds. Further applications and improvements of the reaction are now in progress, and the mechanistic details are being resolved.



Scheme 2. Diastereoselectivities in the addition of RI to α-methylene-γ-phenyl-γ-butyrolactams.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.007.

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