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One-Pot Synthesis of Chiral α-Methylene-γ-lactams with Excellent Diastereoselectivities and Enantioselectivities

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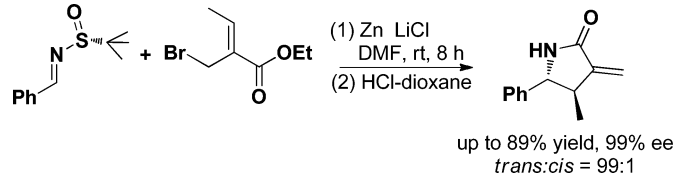
ABSTRACT



An efficient one-pot asymmetric synthesis of highly substituted γ-lactams containing α-methylene groups has been successfully developed. A wide range of γ-lactams could be obtained in high yields with excellent diastereomeric ratios of up to 99:1 in favor of *trans* isomers. In particular, excellent enantioselectivities of the two newly formed stereogenic centers with up to 99% ee were observed.

α-Methylene-γ-lactams are key structural units occurring in a wide variety of biologically active natural products.[1−6] Compared with their isosteric replacement α-methylene-γ-lactones, they are frequently used as DNA polymerase inhibitors, nuclear vitamin D receptor inhibitors, or cellular steroidal inhibitors[7] due to their similar bioactivities in antibacterial, anti-inflammatory, and antianaphylactic properties, however with much lower toxic side effects.[1,8,9] Because of their excellent activities for potential drug candidates as well as their role as significant building blocks for the total synthesis of a series of targeted compounds, the construction of α-methylene-γ-lactam skeletons has received much attention over the past three decades.[10−16] The representative asymmetric synthetic approaches to γ-lactams include the cyclization of nitrogen radicals,[11] the cycloaddition reaction,[12] the transition-metal-catalyzed intramolecular carbenoid C−H insertion,[13] the ring expansion of β-lactams,[14] NHC-catalyzed addition of enals to imines,[15] and tandem sequence aza-Michael/intramolecular nucleophilic substitution.[16] In addition to these methods, there are some indirect approaches based on using chiral reagents such as bis-π-allylpalladium complexes[17] or chiral β-alkoxycarbonylallylboronates,[18] providing the precursors of γ-lactams.

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(1) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rosalski, M. *J. Med. Chem.* **2005**, *48*, 3516.
(2) Cardellina, J. H.; Moore, R. E. *Tetrahedron Lett.* **1979**, *22*, 2007.
(3) Duan, W. Z.; Zhang, J. T. *Acta Chim. Sin.* **1997**, *32*, 259.
(4) Natio, T.; Honda, Y.; Miyata, O.; Ninomiya, T. *Chem. Pharm. Bull* **1993**, *41*, 217.
(5) (a) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (b) Chauhan, D.; Catley, L.; Li, G.; Podar, K.; Hideshima, T.; Velankar, M.; Mitsiades, C.; Mitsiades, N.; Yasui, H.; Letai, A.; Ovaa, H.; Berkers, C.; Nicholson, B.; Chao, T. H.; Neuteboom, S. T.; Richardson, P.; Palladino, M. A.; Anderson, K. C. *Cancer Cell* **2005**, *8*, 407.
(6) Schwartz, R. E.; Helms, G. L.; Bolessa, E. A.; Wilson, K. E.; Giacobbe, R. A.; Tkacz, J. S.; Bills, G. F.; Liesch, J. M.; Zink, D. L.; Curotto, J. E.; Pramanik, B.; Onishi, J. C. *Tetrahedron* **1994**, *50*, 1675.
(7) Konaklieva, M. I.; Plotkin, B. J. *Mini-Rev. Med. Chem.* **2005**, *5*, 73.
(8) Howie, G. A.; Stamos, I. K.; Cassady, J. M. *J. Med. Chem.* **1976**, *19*, 309.
(9) Belaud, C.; Roussakis, C.; Letourneux, Y.; El Alami, N.; Villiéras, J. *Synth. Commun.* **1985**, *15*, 1233.

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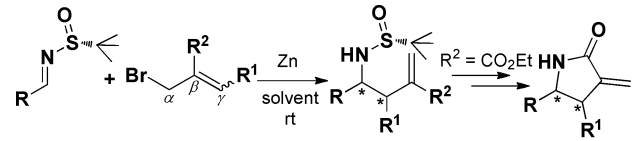
For example, Villiéras[10i] reported a synthesis of γ-lactams with two examples, by addition of β-functional crotylzinc reagents to chiral *N*-α-aminoesters in 60% yield, 92% de, and in 86% yield, 100% de, respectively. However, more steps were needed including reduction and acidic cleavage to remove the auxiliary for achieving the final products. Despite the fact that considerable efforts have been made, a more efficient, reliable, and convenient route to α-methylene-γ-lactams is still in high demand.

Previously, we have reported our achievements about the aza-Barbier reaction for asymmetric synthesis of various important chiral amines.[19] For example, we reported a highly diastereoselective synthesis of chiral homoallylic amines by Zn-mediated allylation of chiral *N*-*tert*-butanesulfinyl imines at room temperature (Scheme 1, **2a**, $R^1 = R^2 = H$). By simply turning the reaction conditions, a remarkable stereocontrol was provided, affording the products *R*/*S*-**3a** in good yields and with up to 99:1 dr.[19a] Moreover, when 3-benzoyloxyallyl bromide (Scheme 1, **2b**, $R^1 = OBz$, $R^2 = H$) or 3-arylallyl bromide (Scheme 1, **2c**, $R^1 = Ar$, $R^2 = H$) was used, a direct α-hydroxyallylation or cinnamylation of imines **1** in a highly stereoselective manner was observed.[19b−d] In the meantime, a dramatic LiCl effect was found on the stereocontrol so that DMF could be used as solvent to replace the unpleasant HMPA.[19d] In our continuous interest to explore the utilities of chiral sulfinyl auxiliary, we envisioned whether it was possible to use β,γ-disubstituted allyl bromide (Scheme 1, **2e**, $R^1 = Me$, $R^2 = CO_2Et$) for setting up another interesting class of homoallylic amines **3** with two adjacent chiral centers simultaneously and which

Scheme 1. Asymmetric Allylation Using Different Allyl Regents



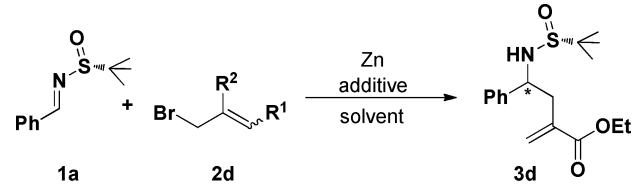
1 2 3 5

a $R^1 = R^2 = H$ allylation
b $R^1 = OBz$, $R^2 = H$ α-hydroxyallylation
c $R^1 = aryl$, $R^2 = H$ cinnamylation
d $R^1 = H$, $R^2 = CO_2Et$ carbethoxyallylation
e $R^1 = Me$, $R^2 = CO_2Et$

by subjecting to further cyclization would yield the chiral α-methylene-γ-lactams **5** in a one-pot varient. In this work, we disclose our success on such an efficient synthesis with high yields and excellent diastereo- and enantioselectivities.

Our initial investigation commenced with the reaction between the model substrates (*R*)-*N*-*tert*-butanesulfinyl imine **1a** and ethyl 2-(bromomethyl)acrylate (Table 1, **2d**, $R^1 = H$, $R^2 = CO_2Et$). According to our previous reports, different kinds of solvents were tested in this reation. Unfortunately, the diastereomeric excesses of products were not satisfactory when THF and DMF were used as solvents (Table 1, entries 1 and 2). When DMF was employed in combination with 2 equiv of

Table 1. Initial Attempts in Reaction Conditions Screening



1a 2d 3d

$R^1 = H$, $R^2 = CO_2Et$

entry[a]	solvent and additive[b]	time (h)	Zn/**2d** (equiv)	yield (%)[c]	de (%)[d]
1	5 mL of THF[e]	8	2	87	−68
2	5 mL of DMF[e]	11	2	94	52
3	5 mL of DMF	11	2	48	96
4	5 mL of HMPA[f]	11	2	23	93
5	2 mL of DMF	12	2	76	99
6	1 mL of DMF	12	2	81	99
7	0.5 mL of DMF	11	2	86	96
8	5 mL of DMF	18	2	45	96
9	1 mL of DMF	75	2	79	97
10	1 mL of DMF	11	3	94	97
11	1 mL of DMF[g]	11	3	88	98

[a] Reaction was performed with 0.2 mmol of **1a**, Zn/**2d**, and additive in dry solvent at rt. [b] 2 equiv of LiCl was used as additive unless otherwise noted. [c] Isolated yield. [d] Determined by ^1H NMR of the product. **3d** was converted to the lactam to determine its configuration and confirm its diastereomeric excess (see Supporting Information). [e] Without any additive. [f] 10 μL of H_2O was used as additive. [g] None-predried DMF was used.

(10) (a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230. (b) Reddy, L. R.; Fournier, J.-F.; Subba Reddy, B. V.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974. (c) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem.* **2004**, *69*, 7765. (d) Lettan, R. B., II; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed* **2008**, *47*, 2294. (e) Krawczyk, H.; Albrecht, L.; Wojciechowski, J.; Wolf, W. M.; Krajewska, U.; Rozalski, M. *Tetrahedron* **2008**, *42*, 6307. (f) Alami, N. E.; Belaud, C.; Villéras, J. *Tetrahedron Lett.* **1987**, *28*, 59. (g) Dembele, Y. A.; Belaud, C.; Hitchcock, P.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351. (h) Dembele, Y. A.; Belaud, C.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511. (i) Nyzam, V.; Belaud, C.; Zammattio, F.; Villiéras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835. (j) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376. (k) Tanaka, K.; Yoda, H.; Kaji, A. *Synthesis* **1985**, 84. (l) Beji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959. (m) Lee, K. Y.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 2007.

(11) (a) Mackiewicz, P.; Furstoss, R.; Wage&, B.; Cote, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746. (b) Callier-Dublanchet, A. C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791.

(12) (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (b) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517. (c) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434. (d) Romero, A.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 2127. (e) Sun, P.-P.; Chang, M. Y.; Chiang, M. Y.; Chang, N. C. *Org. Lett.* **2003**, *5*, 1761. (f) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999.

(13) (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, p 1045. (d) Choi, M. K. W.; Yu, W. Y.; Che, C. M. *Org. Lett.* **2005**, *7*, 1081. (e) Zhou, C. Y.; Che, C. M. *J. Am. Chem. Soc.* **2007**, *129*, 5828.

(14) (a) Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 3369. (b) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981. (c) Park, J.-H.; Ha, J. R.; Oh, S. J.; Kim, J. A.; Shin, D.-S.; Won, T. J.; Lam, Y. F.; Ahn, C. *Tetrahedron Lett.* **2005**, *46*, 1755.

(15) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131.

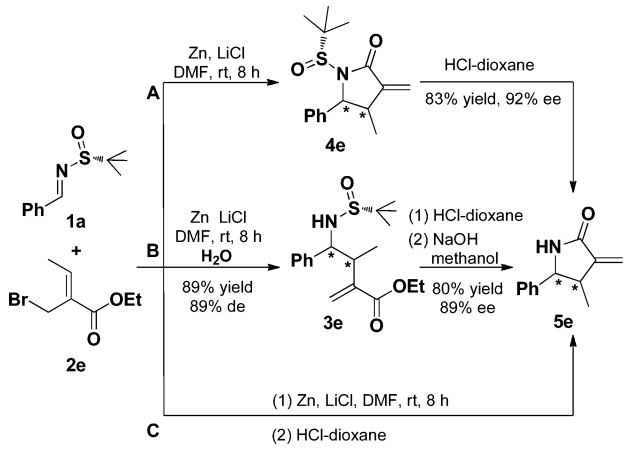
(16) Comesse, S.; Sanselme, M.; Daïch, A. *J. Org. Chem.* **2008**, *73*, 5566.

(17) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3562.

LiCl as an additive, excellent diastereomeric excess (96%) was observed, however with much lower yield (Table 1, entry 3). With the HMPA system, an analogous result was obtained (Table 1, entry 4). On the basis of the eximious diastereomeric excess in the DMF and LiCl system, further study on improving the reaction yield was taken into consideration. By increasing the substrate concentration, to our delight, improved yields were obtained (Table 1, entries 3 vs 5−7). In addition, extension of the reaction time did not seem to affect the yield (Table 1, entry 3 vs 8 and entry 6 vs 9). Remarkably, excellent yield and diastereomeric excess could be achieved simultaneously when the amounts of Zn and allyl bromide **2d** were increased to 3 equiv (Table 1, entry 10). Untreated DMF was also proven to be a suitable solvent, retaining a similar yield and diastereomeric excess (Table 1, entry 11).

Encouraged by the above success, we subsequently turned the extension to γ-methyl substituted allyl bromide by using (*Z*)-ethyl 2-(bromomethyl)butenoate **2e** for investigating the reaction with substrate (*R*)-*N*-*tert*-butanesulfinyl imine **1a** under the optimal reaction conditions (Table 1, entry 10). Although we failed to obtain the expectant product **3e** under the selected conditions, we were pleased to see that **4e**, a ring-closed product of **3e**, was produced. Upon removal of the sulfinyl auxiliary, **4e** could be easily transformed to highly functionalized α-methylene-γ-lactam **5e** in 83% yield and 92% ee (Scheme 2, route A). Then it was found that under

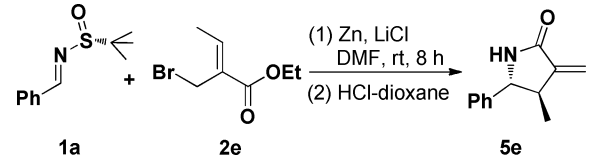
Scheme 2. Different Process to **5e**



the presence of 1−5 equiv of water the same reation occurred to afford **3e** in 89% yield and 89% de. As an alternative way, **3e** could also be cyclized to yield γ-lactam **5e** in about 80% yield (Scheme 2, route B). These results indicated that under the reaction process **3e** was formed first upon the treatment of imine **1a** and allyl bromide **2e**, followed by cyclization to yield the product **4e** immediately, which was then treatd with HCl−dioxane to afford **5e** upon removal of the auxiliary. Thus, the one-pot synthesis of **5e** could be realized (Scheme 2, route C).

Due to the dramatic effect of anhydrous LiCl in this reaction (Table 1), further investigation was taken to optimize the reaction conditions on LiCl loading (Table 2).

Table 2. Effect of the Loading of Anhydrous LiCl



entry[a]	LiCl (equiv)	yield (%)[b]	ee (%)[c]	*trans*:*cis*[c]
1	-	43	12	99:1
2	1	40	32	99:1
3	3	91	96	99:1
4	5	86	99	99:1

[a] Reaction was performed with imine **1a** (0.2 mmol), Zn, and allyl bromide **2e** (0.6 mmol) and anhydrous LiCl in 1 mL of dry DMF at rt and was then treated with 1 N HCl−dioxane (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

As shown in Table 2, very poor result (43% yield and 12% ee) was observed when the reaction occurred in the absence of LiCl (Table 2, entry 1). The presence of LiCl exerted a remarkable impact on enantioselectivities (Table 2, entries 1−4). The best result was given when 5 equiv of LiCl was used where **5e** was obtained in 99% ee and 99:1 dr (Table 2, entry 4).

The relative configuration of **5e** was established to be *trans* by NOE analysis. Since the attempt to have the single crystal of **5e** was unsuccessful, it was turned to use its precursor **4e** or analogues. Fortunately, with the crystal of the analogue **4m** obtained, the absolute configuration of the two newly generated stereocenters in **4m** was unambiguously determined to be (9*R*,10*R*) (Figure 1). Thus, treatment of (*R*)-*N*-*tert*-butanesulfinyl imine **1a** with (*Z*)-ethyl 2-(bromomethyl) butenoate **2e** in the presence of

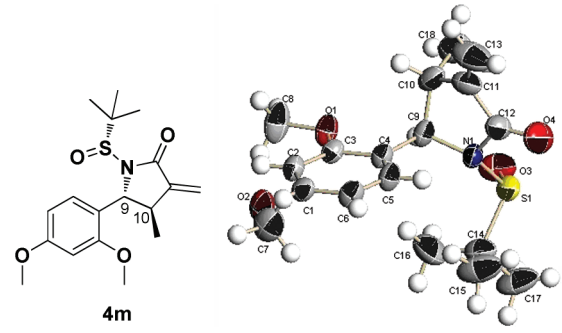


Figure 1. X-ray crystal structure of **4m**.

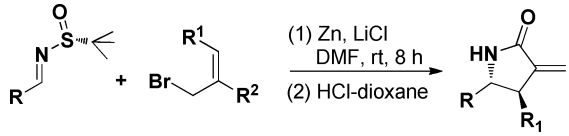
(18) (a) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villiéras, J. *Tetrahedron* **2008**, *64*, 2441. (b) Elford, T. G.; Hall, D. G. *Tetrahedron Lett.* **2008**, *49*, 6995.

(19) (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (b) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (c) Liu, M.; Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Chem.—Eur. J.* **2009**, *15*, 10217. (d) Liu, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, DOI: 10.1039/C0CC03230A.

3 equiv of Zn and 5 equiv of LiCl at room temperature in DMF followed by treatment of 1 N HCl could give almost pure (*R*,*R*)-*trans*-**5e** in a one-pot manner.

After successful establishment of the reaction conditions for the one-pot synthesis of α-methylene-γ-lactam, we paid attention to the investigation of the reaction generality. As summarized in Table 3, a variety of (*R*)-*N*-*tert*-butanesulfinyl imines **1** were examined to react with allzyl bromide **2** in DMF in the presence of Zn (3 equiv) and LiCl (5 equiv). Gratifyingly, all reactions proceeded smoothly at room temperature to afford the expected products **5** with excellent enantioselectivities (up to 99% ee) and diastereoselectivities as well (*trans:cis* = 97:3 to 99:1). Good yields were observed in the cases of aromatic and heterocyclic substrates. Both electron-donating and -withdrawing groups on the phenyl ring of imines did not seem to affect the yields and stereoselectivities significantly (Table 3, entries 1−2 and 5−13). As an exception, the substrate with a 4-CF_3 substituent afforded relatively lower yield due to its low reactivity in cyclization but still retained the 96% enantiomeric excess (Table 3, entry 14). More interestingly, when aliphatic substrates were subjected to the reaction, the same levels of excellent enantioselectivities were observed, albeit the isolated yields were somehow moderate with slow conversion (Table 3, entries 3−4 and 15−17).

Table 3. Diastereoselective Synthesis of α-Methylene-γ-lactams[a]



1 **2d** R^1 = H, R^2 = CO_2Et **2e** R^1 = Me, R^2 = CO_2Et **5**

entry[b]	1	R	2	5	yield (%)[c]	*trans:cis*[d]	ee (%)[d]
1	**1a**	C_6H_5	**2d**	**5a**	85	-	97
2	**1b**	4-$MeOC_6H_4$	**2d**	**5b**	77	-	95
3	**1c**	$C_6H_5CH_2CH_2$	**2d**	**5c**	70	-	98
4	**1d**	cyclohexyl	**2d**	**5d**	69	-	98
5	**1a**	C_6H_5	**2e**	**5e**	86	99.5:0.5	99
6	**1b**	4-$MeOC_6H_4$	**2e**	**5f**	75	99.8:0.2	98
7	**1e**	β-naphthyl	**2e**	**5g**	82	99.5:0.5	99
8	**1f**	2-furanyl	**2e**	**5h**	89	96.6:3.4	99
9	**1g**	2-$CH_3C_6H_4$	**2e**	**5i**	82	98.8:1.2	98
10	**1h**	4-$CH_3C_6H_4$	**2e**	**5j**	85	99:1[e]	95
11	**1i**	4-BrC_6H_4	**2e**	**5k**	79	99:1[e]	98
12	**1j**	4-FC_6H_4	**2e**	**5l**	73	97.1:2.9	98
13	**1k**	2,4-$(MeO)_2C_6H_3$	**2e**	**5m**	78	99.7:0.3[f]	94
14	**1l**	4-$CF_3C_6H_4$	**2e**	**5n**	51	99.6:0.4[f]	96
15	**1c**	$C_6H_5CH_2CH_2$	**2e**	**5o**	59	99.4:0.6	92
16	**1m**	$C_6H_5CH{=}CH$	**2e**	**5p**	70	99.1:0.9	92
17	**1n**	$(CH_3)_2CHCH_2$	**2e**	**5q**	64	98.2:1.8	95

[a] In most cases, uncyclized product was found in a minor amount (about 5−10%). [b] Reaction was performed with imine **1** (0.2 mmol), Zn, and allyl bromide **2** (0.6 mmol) and anhydrous LiCl (1.0 mmol) in 1 mL of dry DMF at rt and was then treated with 1 N HCl−dioxane (0.5 mL). [c] Isolated yield. [d] Determined by chiral HPLC analysis unless otherwise noted. [e] Determined by ^1H NMR of the product.[18b] [f] Determined by LC-MS analysis.

In summary, we have developed an efficient and facile one-pot approach for the asymmetric synthesis of highly substituted γ-lactam compounds containing α-methylene groups through Zn-promoted aza-Barbier-type allylations of (*R*)-*N*-*tert*-butanesulfinyl imines with allzyl bromide in DMF at room temperature. The reaction is well-tolerated; various aromatic and aliphatic imines could act as suitable substrates and display excellent diastereo- and enantioselectivities. Our access to chiral α-methylene-γ-lactams, which is a key scaffold in a wide variety of bioactive natural products and synthetic medicines, provides a valuable tool for synthetic chemistry.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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