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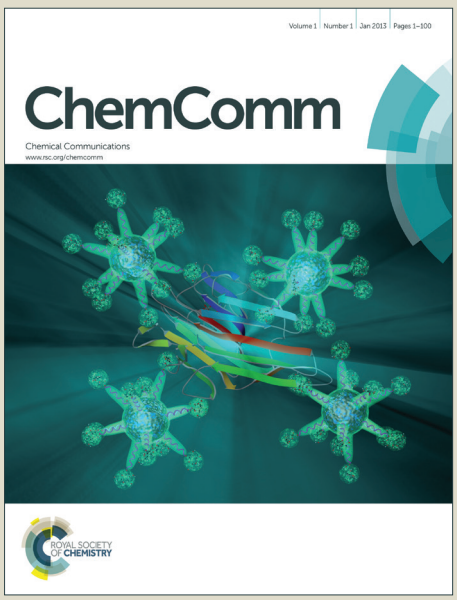

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Diastereoselective Synthesis of α-(Aminomethyl)-γ-butyrolactones via a Catalyst-free Aminolactonization

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An auto-catalytic domino reaction, presumably involving an aza-Michael reaction, proton transfer, and lactonization, furnishing α-(aminomethyl)-γ-butyrolactones in near quantitative yields and excellent diastereoselectivity is described.

The aza-Michael reaction is one of the most useful tools for the production of β-aminocarbonyl compounds,[1] and allows access to pharmacologically and synthetically important functionalities such as β-amino acids,[2] -lactams,[3] and -lactones.[4] Despite their nucleophilicity, amines do not readily undergo spontaneous aza-Michael reactions with typical acceptors, requiring instead the use of high temperatures, or catalytic acceleration.[1] A challenge encountered in designing promoters for this reaction is common: amines, with their high Lewis basicity, act as catalyst poisons by competitively displacing receptors from Lewis acids, rendering the latter unavailable for substrate activation.[5] In response to this, less customary catalysts such as *f*-block element[6] and perchlorate salts[7] have been developed, but they inherently suffer from setbacks such as high cost. Accordingly, newer methods for aza-Michael reactions are still being pursued.

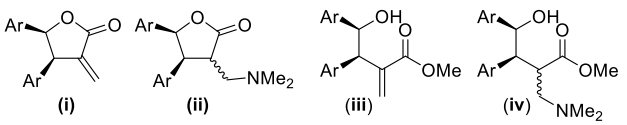
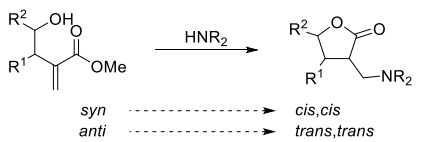


Figure 1 NF-κB Inhibitors

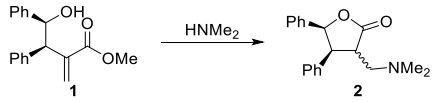
As part of our ongoing program aimed at developing NF-κB inhibitors for the treatment of pancreatic cancer, we have reported on the potency of β,γ-diaryl-α-methylene-γ-butyrolactones (**i**, Figure 1)[8] as well as their α-aminomethyl pro-drug versions (**ii**)[9] against three tumorigenic cell lines, Panc-1, MIA PaCa-2, and BxPC-3. In the course of our *in vitro* studies, we observed that the parent 4-hydroxy-2-methylenebutanoates (**iii**) are equipotent to the cyclized versions (**i**). Attempts to prepare the corresponding 2-aminomethyl-4-hydroxylactones (**iv**) resulted in a tandem amination-lactonization (aminolactonization) reaction, yielding the α-aminomethyl lactones in essentially quantitative yields and diastereoselectivities (Scheme 1).The details of the catalyst-free aminolactonization and a possible mechanism involving a tandem aza-Michael reaction, intramolecular proton transfer, and lactonization, are described herein.



Scheme 1 Aminolactonization of γ-hydroxybutanoates

The addition of an appropriate amine to *syn*-4-hydroxy-2-methylene-3,4-diphenylbutanoate **1** in methanol resulted in the direct formation of the aminated lactone **2**. Excited by these initial results, we sought to develop this tandem transformation, and chose to further explore the reaction of Me_2NH with **1** (Table 1). Upon exposure to Me_2NH in THF, the complete consumption of **1** occurred within 30 h to furnish **2** in >99:1 diastereomeric ratio (dr) in moderate yield (entry 1). A complete parameter optimization was then performed and it was discovered that protic solvents (Entries 4, 9-10) drastically enhanced both the reaction rate and yield. Under the optimized conditions (Entry 12), **2** was formed in essentialy quantitative yield within 3 h in >99:1 dr.

Table 1 Optimization of aminolactonization parameters

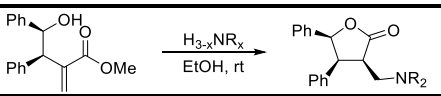


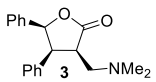
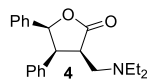
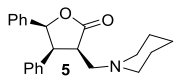
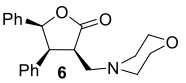
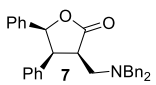
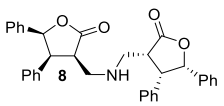
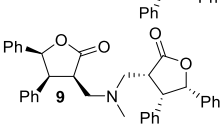
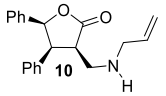
1 2

Entry	Solvent	*T* [°C]	Equiv. HNR_2	*t* [h]	Yield [%][a]	dr (syn : anti)[b]
1	THF	25	1.75	30	51	99:1[c]
2	Hexanes	25	1.75	22	98	97:3
3	H_2O	25	1.75	---	NR[d]	---
4	MeOH	25	1.75	1	>99	85:15
5	CH_2Cl_2	25	1.75	11	>99	99:1[c]
6	Et_2O	25	1.75	30	95	90:10
7	PhMe	25	1.75	11	64	99:1[c]
8	MeCN	25	1.75	30	54	68:32
9	*i*-PrOH	25	1.75	11	92	90:10
10	EtOH	25	1.75	3	>99	95:5
11	EtOH	25	1.00	3	85	99:1[c]
12	**EtOH**	**25**	**2.00**	**3**	**>99**	**99:1[c]**
13	EtOH	0	2.00	6	>99	99:1[c]
14	EtOH	40	2.00	1.5	>99	84:16
15	EtOH	78	2.00	1.5	87	70:30

[a] Yield of major diastereomer. [b] Measured by ^{1}H NMR. [c] Only one detectable diastereomer. [d] NR = no reaction.

Table 2 Scope of amine nucleophile



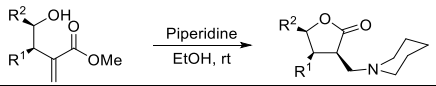
Entry	Amine	Product	d.r.[a]	Yield [%][b]
1	$HNMe_2$		99:1	99
2	$HNEt_2$		99:1	99
3			99:1	99
4			99:1	99
5	$HNBn_2$		99:1	99[c]
6	H_3N[d]		92:8	91
7	H_2NMe[e]		99:1	44
8			99:1	99[f]

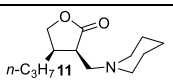
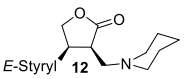
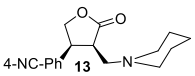
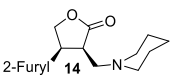
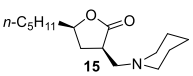
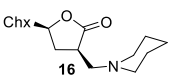
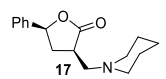
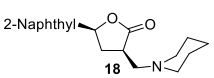
[a]Measured by ^{1}H NMR; refers to the α,β-relationship. [b]Yield without additional purification. [c] Bn_2NH required varying reaction times. [d]33% aq. soln. [e]2.0 M in THF. [f]Isolated via column chromatography.

The scope of amine allowance in this reaction was then determined (Table 2); a wide variety of secondary amines were well tolerated (Entries 1-6). While the use of NH_3 and $MeNH_2$ resulted in the non-*meso* dimers shown (Entries 6-7), allylamine furnished only the monomeric product **10** (Entry 8). Gratifyingly, this atom economical process required no purification beyond the simple removal of reaction volatiles.

We then examined the effects of β- and γ-substitution on the lactonization (Table 3). To this end, the optimized reaction conditions were extended to molecules with substitutions at only the β- (entries 1-4) or γ-position (entries 5-8). Excepting for **14**, consistent dr values favoring the *cis*-isomer (as confirmed by ^{1}H NOE analysis) were obtained.

Table 3 Stereochemical outcomes of aminolactonization reactions

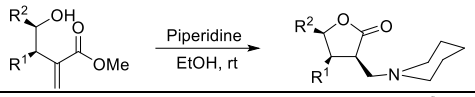


Entry	Butanoate R^1	Butanoate R^2	Product	d.r.[a]	Yield [%][b]
1	*n*-C_3H_7	H		74:26	70
2	*E*-Styryl	H		79:21	76
3	4-NC-C_6H_4	H		79:21	58
4	2-Furyl	H		91:9	79
5	H	*n*-C_5H_{11}		86:14	74
6	H	Chx		87:13	87
7	H	Ph		83:17	78
8	H	2-Naphthyl		84:16	78

[a]Measured by ^{1}H NMR. [b]Isolated yield of major diastereomer

We demonstrated the generality of the aminolactonization by treating a variety of β,γ-disusbtituted-α-methylene-γ-hydroxy esters with piperidine (Table 4). Near-quantitative yields and very high dr values were obtained for almost all of the conversions. All of the *syn*-butanoates furnished the *cis*,*cis*-lactones (Entries 4-7 & 9), while *anti*-**1** gave *trans*,*trans*-compound **28** in quantitative yield and near-perfect dr (Entry 10). Even tertiary alcohols underwent aminolactonization very well (Entries 2-3). The *cis*-methyl of the isobutenyl group (Entry 8) inhibited this reaction even at elevated temperatures, as only the addition product **26** was formed. The assignation of culpability to this group was confirmed by the facility observed in the formation of **27** (Entry 9). The success in forming **19** probably indicates that the Thorpe-Ingold effect[14] is not causing aminolactonization.

Table 4 Substrate scope for aminolactonization



Entry	Product	d.r.[a]	Yield [%][b]
1	X= H, Y= H — **19**	---	93
2	X= Me, Y= Me — **20**	---	96
3	**21**	---	96
4	4-Me-Ph, 4-MeO-Ph — **22**	99:1	99
5	TBSO, 3-Br-Ph — **23**	93:7	92
6	4-MeS-Ph — **24**	92:8	92
7	BnO, AcO, 2-Br-Ph — **25**	99:1	99
8	OH, 4-Br-Ph, OMe — **26**	75:25	78[c]
9	4-Br-Ph — **27**	98:2	98
10	Ph, Ph — **28**	99:1	99

[a]Measured by ^{1}H NMR; refers to the α,β-relationship. [b]Yield of major diastereomer. [c]Combined yield of diastereomers.

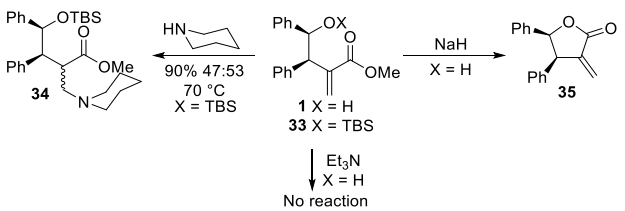
We were interested in forming other ring sizes as well (Table 5). Accordingly, we attempted the formation of a propiolactone and valerolactone (Entries 1-2), but only addition took place (the addition of 1°-amines to Baylis-Hillman adducts is known[11]). These results suggest that this methodology is currently limited to butyrolactone formation. Despite this setback, we examined this reaction with other nucleophiles, carefully choosing the latter to be incapable of readily affecting direct alcohol deprotonation. To this end, we found that dimethyl malonato and triethyl phosphonoacetato anions readily underwent the equivalent domino reactions with **1**, furnishing only the *cis*,*cis*-diastereomers (**31** and **32**, respectively). Expectedly, rapid epimerization of the phosphonoacetitic proton occurred, resulting in an intractable, 1:1 diastereomeric mixture of **32**.

Table 5 Examination of other nucleophiles and ring sizes

Entry	Product	d.r.[a]	Yield [%]
1	OH, O, Ph, OMe, NMe$_2$ — **29**	83:17	57
2	OH, O, OMe, N — **30**	46:54	99[b]
3	Ph, O, CO$_2$Me, Ph, CO$_2$Me — **31**	99:1	86
4	Ph, O, O, P(OEt)$_2$, Ph, CO$_2$Et — **32**	99:1	73

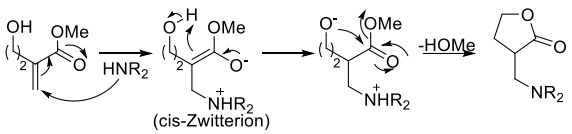
[a]Measured by ^{1}H NMR analysis; refers to the α,β-relationship. [b]Combined yield of diastereomers.

The success and unprecedented nature of this aminolactonization encouraged us to examine both the cause of the reaction's exceptional diastereoselectivity, and, more importantly, the facility of the reaction. To address these questions, the aminolactonization of the TBS-protected ester **33** was attempted (Scheme 2). No reaction took place at rt, but after heating to 70 °C for 24 h, a 90% yield of the aza-Michael product **34** was observed with limited dr. As silylation attenuates *O*-nucleophilicity and eliminates H-bonding ability, it likely suggests that there exists some internal activation which catalyzes this reaction,[10] as well as that a cyclic transition state controls the diastereoselectivity.



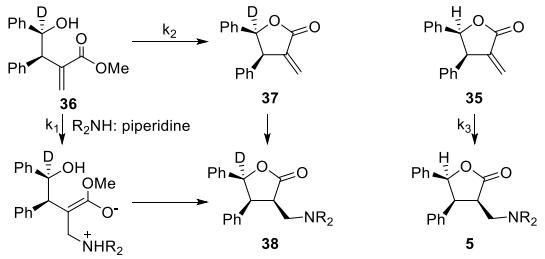
Scheme 2 Probes for the mechanism

A possible explanation for the observed cyclization is a reaction sequence involving a base-promoted lactonization followed by an aza-Michael reaction. Indeed, the superior Michael acceptor ability of an *in situ*-formed α-methylene-γ-butyrolactone could allow for such an aza-Michael reaction with secondary amines to take place at ambient temperature in protic solvents.[12] However, we negated this notion by showing that, while strong bases such as NaH resulted in the lactonization of **1**, Et_3N, which is of a similar basicity to secondary amines, could not (Scheme 2). This led us to postulate a pathway involving an aza-Michael reaction, followed by an intramolecular, *face*-selective protonation of the enolate by the alcohol, and a subsequent lactonization of the thus-formed alkoxide (Scheme 3).



Scheme 3 Proposed intramolecular proton transfer mechanism

To further probe the mechanism, we designed a competitive isotopic distribution experiment (Scheme 4). Piperidine was added to a 1:1 mixture of **35** and **36** (the *γ*-deuterio analog of **1**) in ethanol, wherein three outcomes were possible. First, piperidine could simply react with the 'better' Michael acceptor **35**. In this case ($k_3>k_1$ or k_2), it would be necessary that little deuterium incorporation into the product mixture be observed. The second possibility was for **36** to be converted into the deuterated lactone **37** *in situ*, followed by a conjugate addition ($k_2>k_1$ or k_3). Were this occurring, a buildup of **37** would occur, and piperidine would undergo a subsequent addition onto both of the isotopically differentiated lactones, giving a nearly 1:1 ratio of **38**:**5**, and a ≈50% deuterium incorporation by ^{1}H NMR. In the third scenario, an aza-Michael reaction onto **36** would occur rapidly, followed by the lactonization reaction ($k_1>k_2$ or k_3). Were this pathway correct, it would necessitate a near-complete incorporation of deuterium into the product. After 30 min, the volatile components were removed from the reaction mixture; ^{1}H and ^{2}H NMR analysis indicated a>99% incorporation of deuterium into the *γ*-position of the resulting aminolactone, indicating that **38** had formed instead of **5**, thereby supporting our postulation.



Scheme 4 Isotopic competition experiment.

While it cannot be definitively ruled out, the fact that the reaction proceeds in excellent diastereoselectivity even in aprotic solvents such as CH_2Cl_2 and toluene (Table 1, entries 5 and 7) as well as that the reaction of **33** resulted only in uncyclized product **34** suggests that the solvent might not be involved in the direct protonation of the enolate. If present, a role played by the acidic ammonium proton in scheme 3 may or may not be immaterial. However, our postulated mechanism satisfactorily clarifies the observed diastereoselectivities (see electronic supplementary information).

In conclusion, we have developed a remarkably mild and efficient procedure for the synthesis of *α*-(aminomethyl)-γ-butyrolactones. This novel reaction, which occurs in nearly quantitative yields and with readily predictable and consistent diastereomeric outcomes, offers a highly efficient route to the synthesis of these important bio-active compounds.

Acknowledgments

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Notes and references

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Electronic Supplementary Information (ESI) available: Full experimental and characterization data. See DOI: 10.1039/c000000x/

1 (a) D. Enders, C. Wang and J. X. Liebich, Chem. Eur. J. 2009, 15, 11058; (b) J. L. Vicario, D. Badía, L. Carrillo, J. Etxebarria, E. Reyes and N. Ruiz, *Org. Prep. Proced. Int*. 2005, **37**, 513; (c) L. -W. Xu and C. –G. Xia, *Eur. J. Org. Chem*. 2005, 633.
2 E. Juaristi, in Enantioselective Synthesis of β-Amino Acids Wiley-VCH, Weinheim, 1997.
3 P. A. Magriotis, *Angew. Chem. Int. Ed*. 2001, **40**, 4377.
4 S. Neelakantan, S. Nasim, M. L. Guzman, C. T. Jordan and P. A. Crooks, *Bioorg. Med. Chem. Lett*. 2009, **19**, 4346.
5 M. Kawatsura and J. F. Hartwig, *Organometallics* 2001, **20**, 1960.
6 (a) G. Bartoli, M. Bosco, E. Marcantoni, M. Petrini, L. Sambri and E. Torregiani, *J. Org. Chem*. 2001, **66**, 9052; (b) G. Jenner, *Tetrahedron Lett*. 1995, **36**, 233.
7 N. Azizi and M. R. Saidi, *Tetrahedron* 2004, **60**, 383.
8 P. V. Ramachandran, D. Pratihar, H. N. G. Nair, M. Waters, S. Smith, M. T. Yip-Schneider, H. Wu and C. M. Schmidt, *Bioog. Med. Chem. Lett*. 2010, **20**, 6620.
9 P. V. Ramachandran, D. R. Nicponski, H. N. G. Nair, M. A. Helppi, P. D. Gagare, C. M. Schmidt and M. T. Yip-Schneider, *Bioorg. Med. Chem. Lett*. 2013, **23**, 6911.
10 Only limited H-bonding typically exists in γ-hydroxycarbonyl compounds. L. L. McCoy and D. Mal, *J. Org. Chem*. 1984, **49**, 939.
11 The *anti*-diastereomer was the major product, as determined by comparison with reported values: O. Prien, K. Rölfing, M. Thiel and H. Künzer, *Synlett* 1997, 325.
12 Many examples appear in the literature. For one such case, see Ref 4.
13 Such interactions with the vinylic ether are unlikely, as the Bürgi-Dunitz angle of attack necessitates a dihedral angle approaching a gauche conformation. H. B. Bürgi, J. D. Dunitz, J. M. Lehn and G. Wipff, *Tetrahedron* 1974, **30**, 1563.
14 R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc*. 1915, **107**, 1080.

