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"On water" catalytic enantioselective sulfenylation of deconjugated butyrolactams

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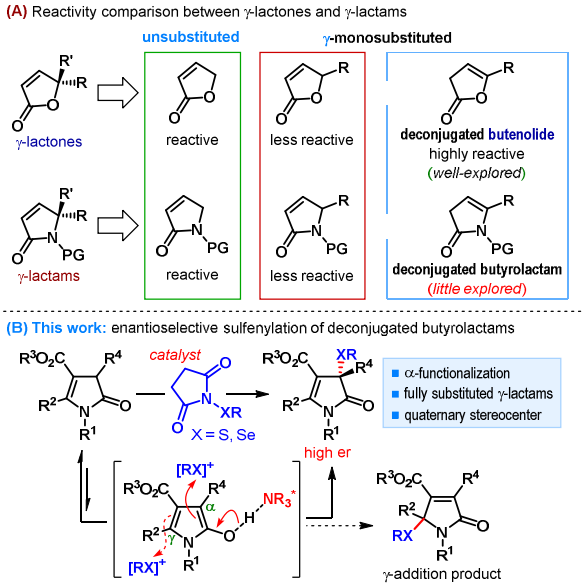
The first catalytic enantioselective α-sulfenylation of deconjugated butyrolactams has been developed using dimeric cinchona alkaloids as the catalyst in water-enriched reaction medium. Highly substituted and densely functionalized γ-lactams, bearing a quaternary stereogenic center, are produced with up to 99.5:0.5 er. The applicability of the same catalyst system for enantioselective α-selenylation and formal vinylogous γ hydroxylation of deconjugated butyrolactam has also been described.

Introduction

γ-Lactams and their derivatives are structural motifs often found in a wide variety of natural products and are of principal interests in medicinal chemistry.[1] Therefore, enantioselective construction of structurally diverse γ-lactams remain a subject of general interest. 2-Silyloxypyrroles[2] and *N*-Boc α,β-unsaturated γ-butyrolactam[3] are the two most commonly employed building blocks for enantioselective synthesis of γ-lactams. In spite of their widespread utility, the methods involving the former suffer from narrow substrate scope while the applicability of the latter is limited to the synthesis of γ-monosubstituted γ-lactams. The corresponding γ-monosubstituted α,β-unsaturated butyrolactams (Scheme 1A), owing to their considerably lower acidity, have not found application in catalytic enantioselective synthesis until a very recent report by Maruoka and co-workers.[4] Although the problem of low acidity of γ-monosubstituted conjugated butyrolactams has been addressed by the Maruoka group using a fairly strong base under phase-transfer catalysis, the scope of this vinylogous Michael reaction is restricted to γ-aryl or heteroaryl substituted butyrolactams.[4]

In the domain of butenolides – the oxo-analogs of γ-lactams, a similar problem has been tackled through the introduction of γ-substituted β,γ-unsaturated butyrolactones (deconjugated butenolides) as a highly reactive class of nucleophiles (Scheme 1A).[5] A wide range of catalytic enantioselective reactions involving deconjugated butenolides have been reported during the past few years.[6] In contrast, the corresponding deconjugated butyrolactams, although reported in the literature,[7] have rarely been used as nucleophile.[4] In fact, enantioselective reactions involving deconjugated butyrolactams remain sporadic.[8]



Scheme 1 Direct enantioselective functionalization of γ-lactams.

In analogy with deconjugated butenolides, we postulated that enolization of butyrolactam should be possible under the influence of a Brønsted basic tertiary amine catalyst. The resulting pyrrolyl dienolate could then react with an electrophile in a regiodivergent manner either through α- or γ-position (Scheme 1B). This strategy holds the potential of generating highly substituted and densely functionalized γ-lactams containing a quaternary stereogenic center. Controlling regioselectivity would obviously be the key since a mixture of α- and γ-addition products would be of little value.

Prevalence of sulfur-containing compounds in many synthetic drugs and bioactive natural products[9] inspired the development of numerous enantioselective C–S bond forming

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reactions.[10] However, to the best of our knowledge, sulfenylation of butyrolactams has never been reported, let alone an enantioselective variant.[11] Herein we report the first example of the use of deconjugated butyrolactams as nucleophile in catalytic enantioselective carbon–heteroatom bond forming transformations (Scheme 1B).

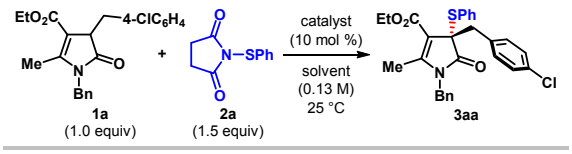
Results and discussion

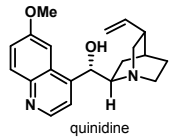
At the outset of our investigation, sulfenylation of tetrasubstituted β,γ-unsaturated butyrolactam **1a** with *N*-(phenylsulfanyl)succinimide (**2a**) was selected as the model reaction (Table 1). Our initial focus was on the Brønsted basic catalysts, employed earlier for various enantioselective reactions of deconjugated butenolides by our group and others.[5,6] Bifunctional tertiary amino(thio)ureas and squaramides, although displayed decent catalytic activity for the sulfenylation of **1a**, failed to induce appreciable level of enantioselectivity.[12] Nevertheless, we were delighted to observe that in all these cases, α-sulfenylation product was formed exclusively without a trace of γ-addition. This regioselectivity trend stands in sharp contrast to those reported earlier for deconjugated butenolides, where γ-addition predominates.[5,6,13] While modest enantioselectivity was observed with quinidine as the catalyst in CH_2Cl_2 at 25 °C, 10 mol% of its dimer $(QD)_2PHAL$ furnished the product with significantly improved er under the same reaction conditions (entries 2-3). A comprehensive solvent survey revealed *tert*-butylbenzene (*t*-BuPh) as the optimal in terms of enantioselectivity, even though the reaction rate suffered drastically (entry 5). In an attempt to address the sluggish rate of this sulfenylation process, we speculated the use of water as a co-solvent which is known to accelerate certain organic reactions through "hydrophobic hydration".[14] Additionally, the stoichiometric by-product succinimide may be removed from the organic phase because of its high water solubility.

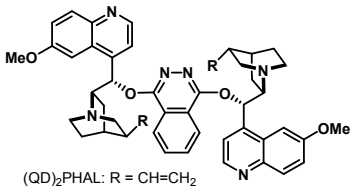
The use of a 1:1 mixture of *t*-BuPh and water as the reaction medium was indeed found to enhance the rate of the reaction considerably without affecting the enantioselectivity, and led to complete conversion of **1a** within 36 h (entry 7). This effect appeared to be more prominent in water-enriched media, and a 1:9 ratio of *t*-BuPh/water turned out to be the optimal with respect to both rate and enantioselectivity (entry 10). On performing the reaction on 0.1 M initial concentration, an improved enantioselectivity (98:2 er) was observed within a reasonable time scale (entry 11). However, further dilution showed a deleterious influence on both reaction rate and er (entry 12). It is interesting to note that the sulfenylation reaction proceeds even more rapidly in aqueous medium[15] and also in brine while maintaining high level of enantioselectivity (entries 13-14). The rate deceleration in antihydrophobic aqueous $LiClO_4$ is often used as an indication for hydrophobic hydration effect.[14] The sulfenylation reaction, when conducted in saturated aqueous $LiClO_4$ solution, required 80 h for completion as opposed to 6 h in water and 12 h in brine (cf. entry 15 with entries 13-14). These observations tentatively point to the possible hydrophobic hydration effect operative for this sulfenylation reaction in water-enriched media.

The scope and limitations of this sulfenylation protocol was then tested under the catalyst and reaction conditions optimized for **1a** and **2a** (Table 1, entry 11). As shown in Table 2A, an array of butyrolactams having α-substituent with diverse steric and electronic demands were well accommodated to deliver the α-sulfenylated products generally with high yields and excellent enantioselectivities. These substituents include benzylic (**3aa**-**ia**) as well as linear (**3ja**) and branched (**3la**) aliphatics. However, α-isobutyl containing butyrolactam (**3k**) remained unreacted under our reaction conditions, presumably due to increased steric crowding near the reaction site. Our protocol was amenable to different aromatic sulfenyl donors (**2b-f**), furnishing products with good to high yields and excellent enantioselectivities (Table 2B). The aliphatic sulfenyl donors (**2g**-**h**) were found to be unreactive under our reaction conditions and hence mark a current limitation of our protocol. Deconjugated butyrolactams bearing various substituents at the γ-position (**1m**-**p**), on ester (**1q**) as well as on nitrogen were also tolerated and afforded the products generally in good yields and with moderate to high er (Table 2C). In fact, the product derived from *N*-unprotected butyrolactam (**3ta**) was also obtained in high yield, albeit with moderate er.

Table 1 Optimization of reaction conditions: effect of water







Entry	Catalyst	Solvent	t/h[a]	er[b]
1	None	CH_2Cl_2	48[c]	-
2	quinidine	CH_2Cl_2	72	62.5:37.5
3	$(QD)_2PHAL$	CH_2Cl_2	24	88:12
4	$(QD)_2PHAL$	PhMe	96	93.5:6.5
5	$(QD)_2PHAL$	*t*-BuPh	96	96.5:3.5
6	$(DHQD)_2PHAL$	*t*-BuPh	96	93.5:6.5
7	$(QD)_2PHAL$	*t*-BuPh/H_2O (1:1)	36	96.5:3.5
8	$(QD)_2PHAL$	*t*-BuPh/H_2O (3:1)	72	97:3
9	$(QD)_2PHAL$	*t*-BuPh/H_2O (1:3)	36	97:3
10	$(QD)_2PHAL$	*t*-BuPh/H_2O (1:9)	12	96.5:3.5
11[d]	$(QD)_2PHAL$	*t*-BuPh/H_2O (1:9)	24	98:2
12[e]	$(QD)_2PHAL$	*t*-BuPh/H_2O (1:9)	48	97.5:2.5
13	$(QD)_2PHAL$	H_2O	6	96:4
14	$(QD)_2PHAL$	Brine	12	97:3
15	$(QD)_2PHAL$	Sat. aq. $LiClO_4$	80	86.5:13.5

[a] Time required for complete consumption of **1a**. [b] Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase. [c] No conversion of **1a**. [d] Reaction at 0.1 M concentration. [e] Reaction at 0.05 M concentration.

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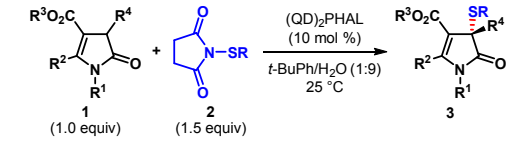
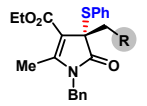
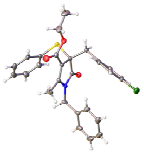
The single crystal X-ray diffraction analysis of **3aa** confirmed its absolute configuration (Table 2A).[16] The configurations of the other products were assigned the same by analogy.

Table 2 Substrate scope of catalytic enantioselective sulfenylation[a]

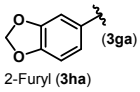


(A)

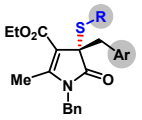




3aa
(CCDC 1549957)

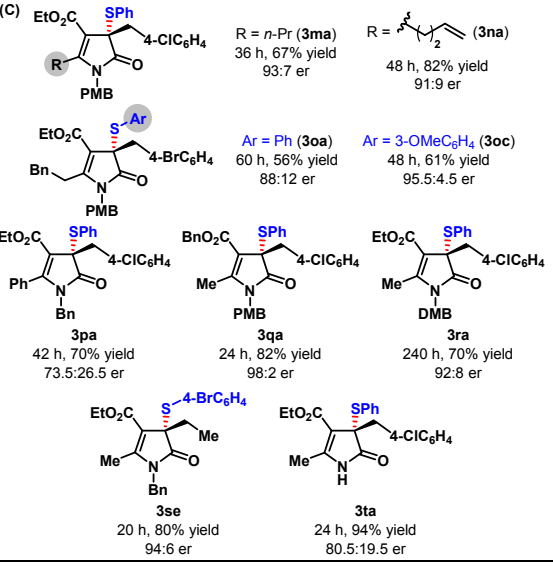
R	*t* [h]	Yield [%]	er
4-ClC$_6$H$_4$ (**3aa**)	24	88	98:2
Ph (**3ba**)	20	87	>98:2
4-CF$_3$C$_6$H$_4$ (**3ca**)	20	89	98:2
4-OMeC$_6$H$_4$ (**3da**)	32	92	97.5:2.5
3-ClC$_6$H$_4$ (**3ea**)	24	87	96:4
2-FC$_6$H$_4$ (**3fa**)	22	90	98:2
 (**3ga**)	24	87	98:2
2-Furyl (**3ha**)	24	80	97.5:2.5
2-Thienyl (**3ia**)	20	90	97.5:2.5
n-Pent (**3ja**)	40	82	96.5:3.5
i-Pr (**3ka**)	48	<5	-
i-Bu (**3la**)	48	81	97.5:2.5

(B)



Ar	R	3	*t* [h]	Yield [%]	er
Ph	2-FC$_6$H$_4$	**3bb**	20	86	99.5:0.5
Ph	3-OMeC$_6$H$_4$	**3bc**	24	84	98.5:1.5
4-ClC$_6$H$_4$	2-Naphthyl	**3ad**	44	76	96.5:3.5
4-ClC$_6$H$_4$	4-BrC$_6$H$_4$	**3ae**	24	93	97.5:2.5
4-ClC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	**3af**	20	85	97.5:2.5
4-ClC$_6$H$_4$	Bn	**3ag**	48	<5	-
4-ClC$_6$H$_4$	*c*-Hex	**3ah**	48	<5	-

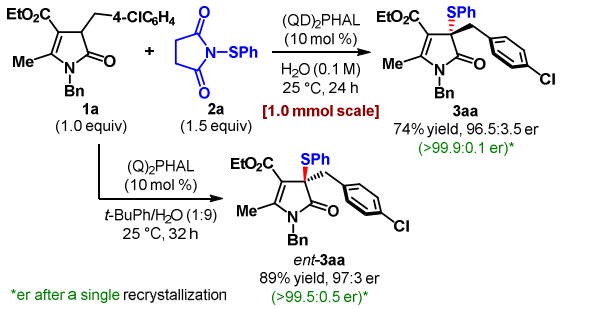
(C)



[a] Reactions were carried out on a 0.1 mmol scale. Yields correspond to the isolated yield. Er was determined by HPLC analysis on a chiral stationary phase. PMB = *p*-methoxybenzyl. DMB = 2,4-dimethoxybenzyl.

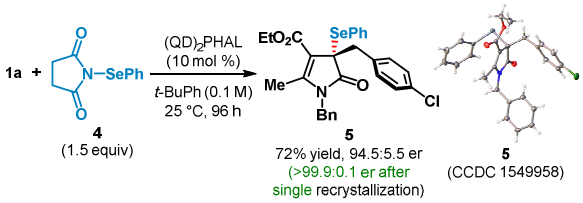
The scalability of this protocol is demonstrated by conducting the reaction between **1a** and **2a** in 1.0 mmol scale using water as the reaction medium (Scheme 2). The product **3aa**, which was initially formed with 96.5:3.5 er, could be recrystallized to deliver essentially enantiopure product.

An important aspect of a catalytic enantioselective protocol is to provide access to both product enantiomers. To our delight, the opposite product antipode *ent*-**3aa** was formed in 89% yield and with 97:3 er using the related pseudoenantiomeric quinine dimer (Q)$_2$PHAL as the catalyst under otherwise standard reaction conditions (Scheme 2).



Scheme 2 "On water" sulfenylation in mmol scale and access to enantiomeric product.

We reasoned that the catalyst and reaction conditions developed for the enantioselective sulfenylation reaction (Table 2) might be suitable for an analogous α-selenylation of deconjugated butyrolactams. However, the instability of the related reagent *N*-(phenylseleno)succinimide **4** in water forced us to use *t*-BuPh as the reaction medium. Under these modified conditions, the α-selenyl butyrolactam **5** was formed in 72% yield and with 94.5:5.5 er (Scheme 3). A single recrystallization from *n*-hexane/CHCl$_3$ not only led to nearly enantiopure **5**, but also allowed us to establish its absolute configuration through X-ray diffraction analysis.[16] The same sense of stereoinduction observed for sulfenylation and selenylation points to a mechanistic resemblance of these two reactions.



Scheme 3 Catalytic enantioselective selenylation of deconjugated butyrolactam.

Having successfully developed the protocols for catalytic enantioselective α-sulfenylation and α-selenylation of deconjugated butyrolactams, we turned our attention to demonstrate the synthetic usefulness of the respective products. The α-selenyl butyrolactam **5**, upon exposure to *m*CPBA in a mixture of CH_2Cl_2 and water, rapidly rearranged to a γ-hydroxylated α,β-unsaturated butyrolactam **6** with retention of configuration, as confirmed by X-ray diffraction analysis (Scheme 4A).[16] This enantiospecific heteroatom transposition reaction most likely proceeds via the oxidation of the allylic selenide moiety, embedded in the butyrolactam framework, to the corresponding selenoxide (**7**) followed by a

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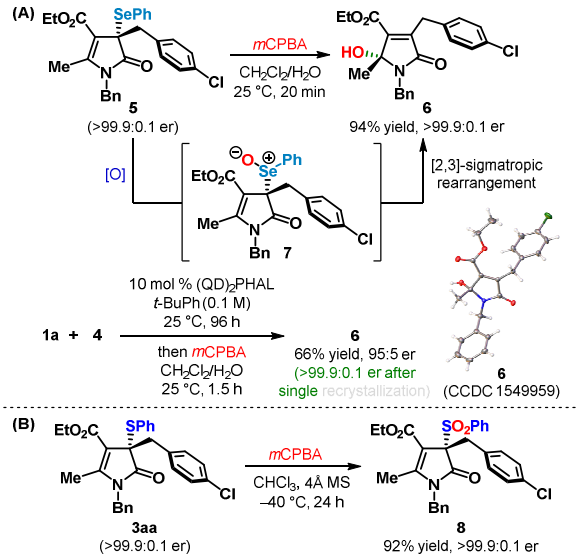
[2,3]-sigmatropic rearrangement.[17] It is possible to perform this reaction in a one-pot manner starting from **1a**, when the product (**6**) was formed in 66% yield with comparable enantioselectivity as the stepwise route. This process represents a formal enantioselective vinylogous γ-hydroxylation of deconjugated butyrolactam – a hitherto unknown transformation. Notably, γ-hydroxy γ-lactams represent the core structure of numerous natural products.[18] Even though sulfides are known to undergo the same type of rearrangement,[19] the similar oxidation conditions, when applied to α-sulfenyl butyrolactam **3aa**, led to sulfone **8** in high yield, without any trace of hydroxylation product (Scheme 4B).



Scheme 4 Synthetic elaboration of the products.

Conclusions

In conclusion, deconjugated butyrolactams have been applied for the first time as nucleophile in catalytic enantioselective carbon–heteroatom bond forming transformations. Catalyzed by dimeric cinchona alkaloids in a water-enriched reaction media, this α-sulfenylation protocol delivers highly substituted and densely functionalized γ-lactams, bearing a quaternary stereogenic center, in moderate to high yields and generally with high enantioselectivities. Substantial rate acceleration was observed in water-enriched or aqueous media, possibly due to hydrophobic hydration effect. The suitability of the same catalyst system for enantioselective α-selenylation and formal vinylogous γ-hydroxylation of deconjugated butyrolactam has also been demonstrated.

Acknowledgements

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Notes and references

1 J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134.
2 (a) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian and J. Y. D. J. Dixon, *Nat. Commun.*, 2014, 4479; (b) C. Curti, B. Ranieri, L. Battistini, G. Rassu, V. Zambrano, G. Pelosi, G. Casiraghi and F. Zanardi, *Adv. Synth. Catal.*, 2010, **352**, 2011; (c) H. Suga, H. Takemoto and A. Kakehi, *Heterocycles*, 2007, **71**, 361; (d) M. Frings, I. Atodiresei, Y. Wang, J. Runsink, G. Raabe and C. Bolm, *Chem.–Eur. J.*, 2010, **16**, 4577. For reviews, see: (e) X. Jusseau, L. Chabaud and C. Guillou, *Tetrahedron*, 2014, **70**, 2595; (f) Z. Miao and F. Chen, *Synthesis*, 2012, **44**, 2506; (g) G. Casiraghi, F. Zanardi, L. Battistini and G. Rassu, *Synlett*, 2009, 1525.
3 For selected examples, see: (a) D. Li, Y. Wang, L. Wang, J. Wang, P. Wang, K. Wang, L. Lin, D. Liu, X. Jiang and D. Yang, *Chem. Commun.*, 2016, **52**, 9640; (b) X. Gu, T. Guo, Y. Dai, A. Franchino, J. Fei, C. Zou, D. J. Dixon and J. Ye, *Angew. Chem., Int. Ed.*, 2015, **54**, 10249; (c) Y. Z. Ma, J. Zhang, D. Yang and R. Wang, *Org. Lett.*, 2014, **16**, 5358; (d) X. Jiang, L. Liu, P. Zhang, Y. Zhong and R. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 11329; (e) J. Zhang, X. Liu, X. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 9329; (f) J. Zhang, X. Liu, X. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 3300; (g) A. Ray Choudhury and S. Mukherjee, *Org. Biomol. Chem.*, 2012, **10**, 7313; (h) H. Huang, Z. Jin, K. Zhu, X. Liang and J. Ye, *Angew. Chem. Int. Ed.*, 2011, **50**, 3232; (i) X. Feng, H.-L. Cui, S. Xu, L. Wu and Y.-C. Chen, *Chem.–Eur. J.*, 2010, **16**, 10309; (j) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666.
4 A. Arlt, H. Toyama, K. Takada, T. Hashimoto and K. Maruoka, *Chem. Commun.*, 2017, **53**, 4779.
5 H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu and Y.-C. Chen, *Org. Lett.*, 2010, **12**, 720.
6 For selected examples, see: (a) M. S. Manna, R. Sarkar and S. Mukherjee, *Chem.–Eur. J.*, 2016, **22**, 14912; (b) A. K. Simlandy and S. Mukherjee, *Org. Biomol. Chem.*, 2016, **14**, 5659; (c) V. Kumar and S. Mukherjee, *Chem. Commun.*, 2013, **49**, 11203; (d) Y. Wu, R. P. Singh and L. Deng, *J. Am. Chem. Soc.*, 2011, **133**, 12458; (e) L. Zhou, L. Lin, J. Ji, M. Xie, X. Liu and X. Feng, *Org. Lett.*, 2011, **13**, 3056; (f) A. Quintard, A. Lefranc and A. Alexakis, *Org. Lett.*, 2011, **13**, 1540. Also see: ref. 2a and 2e.
7 (a) Á. Cores, V. Estévez, M. Villacampa and J. C. Menéndez, *RSC Adv.*, 2016, **6**, 39433; (b) D. Kalaitzakis, E. Antonatou and G. Vassilikogiannakis, *Chem. Commun.*, 2014, **50**, 400; (c) D. Kalaitzakis, T. Montagnon, E. Antonatou, N. Bardají and G. Vassilikogiannakis, *Chem.–Eur. J.*, 2013, **19**, 10119.
8 (a) Q. Yuan, D. Liu and W. Zhang, *Org. Lett.*, 2017, **19**, 1144; (b) H. R. Campello, J. Parker, M. Perry, P. Ryberg and T. Gallagher, *Org. Lett.*, 2016, **18**, 4124. For reactions of *in situ* generated deconjugated butyrolactams, see: (c) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796.
9 (a) J.-S. Yu, H.-M. Huang, P.-G. Ding, X.-S. Hu, F. Zhou and J. Zhou, *ACS Catal.*, 2016, **6**, 5319; (b) P. Chauhan, S. Mahajan and D. Enders, *Chem. Rev.*, 2014, **114**, 8807.
10 For pioneering studies, see: (a) S. Sobhani, D. Fielenbach, M. Marigo, T. C. Wabnitz and K. A. Jørgensen, *Chem.–Eur. J.*, 2005, **11**, 5689; (b) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 794.
11 For enantioselective sulfenylation of a related class of nucleophiles - oxindoles, see: (a) C. Wang, X. Yang, C. C. J.

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DOI: 10.1039/C7OB01714F

Loh, G. Raabe and D. Enders, *Chem.–Eur. J.*, 2012, **18**, 11531; (b) Z. Han, W. Chen, S. Dong, C. Yang, H. Liu, Y. Pan, L. Yan and Z. Jiang, *Org. Lett.*, 2012, **14**, 4670; (c) X. Li, C. Liu, X.-S. Xue and J.-P. Cheng, *Org. Lett.*, 2012, **14**, 4374.

12 For comprehensive optimization studies, see the Supporting Information, Part-A.

13 For an example of α-addition, see: B. Wu, Z. Yu, X. Gao, Y. Lan and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2017, **56**, 4006.

14 (a) J. H. Sim and C. E. Song, *Angew. Chem., Int. Ed.*, 2017, **56**, 1835; (b) H. Y. Bae and C. E. Song, *ACS Catal.*, 2015, **5**, 3613; (c) H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee and C. E. Song, *Chem. Commun.*, 2011, **47**, 9621. For a review, see: (d) R. Breslow, *Acc. Chem. Res.*, 2004, 37, 471.

15 (a) M. Raj and V. K. Singh, *Chem. Commun.*, 2009, 6687; (b) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.

16 CCDC 1549957-1549959 contain the crystallographic data for **3aa**, **5** and **6**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

17 L. C. Hess, and G. H. Posner, *Org. Lett.*, 2010, **12**, 2120.

18 B. Nay, N. Riache and L. Evanno, *Nat. Prod. Rep.*, 2009, **26**, 1044.

19 (a) D. A. Evans, G. C. Andrews and C. L. Sims, *J. Am. Chem. Soc.*, 1971, **93**, 4956; (b) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4869.