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Optically Active Bicyclic N-Heterocycles by Organocatalytic Asymmetric Michael Addition/Cyclization Sequences

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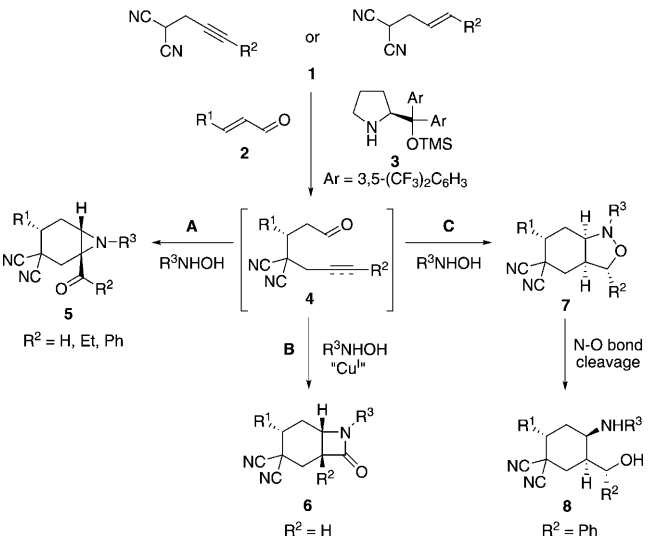
Organocatalysis has over the last decade been established as a powerful tool for numerous enantioselective transformations.[1] Recently, a major effort has been devoted to the development of domino, cascade, and one-pot reactions.[2] These approaches allow the construction of structurally diverse molecules, while minimizing the number of manual operations, thereby saving time, effort, and production costs. Additionally, they are generally considered to be more environmentally friendly, ecological, and sustainable, because of the fewer purification steps than classical stepwise protocols.

Cycloaddition reactions, especially 1,3-dipolar cycloadditions involving nitrones, have proven their potential as powerful synthetic transformations.[3] Owing to the concerted nature of cycloadditions, high levels of stereogenic control are observed, which allow the selective construction of multiple stereocenters in a single reaction step. Furthermore, based on the intrinsic lability of the N–O bond, the heteroatoms of the nitrone introduce useful functionalities in the product, which can be exploited in further syntheses.[4]

We envisioned a one-pot process, in which addition of malononitrile derivatives **1**, with an appropriately tethered alkyne functionality, to an α,β-unsaturated aldehyde **2** would furnish an intermediate that upon condensation with an *N*-aryl hydroxylamine would undergo an intramolecular 1,3-dipolar cycloaddition affording hexahydrobenzo[*c*]isoxazoles. Owing to the inherent ring strain of the five-membered dihydroisoxazole ring, they should be able to undergo a Baldwin rearrangement[5] to the corresponding, densely functionalized aziridine carbonyls **5** (Scheme 1, path A). Moreover, the reaction setup would give access to β-lactams **6** by the Kinugasa reaction,[6] if the cycloaddition step for terminal alkyne functionalized intermediates is carried out in the presence of a Cu^{I} source and a suitable base (Scheme 1, path B). Ideally, the stereocenter created in the initial addition step controls the formation of the other stereocenters in a highly selective manner, giving rise to single diastereoisomers of the optically active products. This highly



Scheme 1. Synthetic outline for the enantioselective organocatalytic one-pot formation of aziridine carbonyls **5**, β-lactams **6**, octahydrobenzo[*c*]-isoxazoles **7**, and 1,3-amino alcohols **8**.

divergent synthesis allows fast access to products such as aziridine carbonyls or β-lactams, which have proven their synthetic usefulness and biological activity.[7] Finally, the application of alkene functionalities in **1** would enable the stereoselective construction of octahydrobenzo[*c*]isoxazoles **7** by a similar addition/cyclization reaction, and the synthesis of 1,3-amino alcohols **8** from **7** through reductive N–O bond cleavage (Scheme 1, path C).[8] To the best of our knowledge, there have been no reports on these sequences in the literature to date.

Herein, we report Michael addition/cycloaddition based one-pot protocols for the highly enantio- and diastereoselective syntheses of aziridine carbonyls **5**, β-lactams **6**, and octahydrobenzo[*c*]isoxazoles **7** in good yields. Furthermore, the formation of optically active 1,3-amino alcohols from **7** and the stereoselective hydrolysis of one of the nitrile substituents in **8** are demonstrated.

To achieve an efficient one-pot protocol, two equivalents of pent-2-enal and malononitrile **1a** (R^2 = H) were allowed to react in dichloromethane with 10 mol% of (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine (**3**) and 10 mol% benzoic acid as catalysts, which pro-

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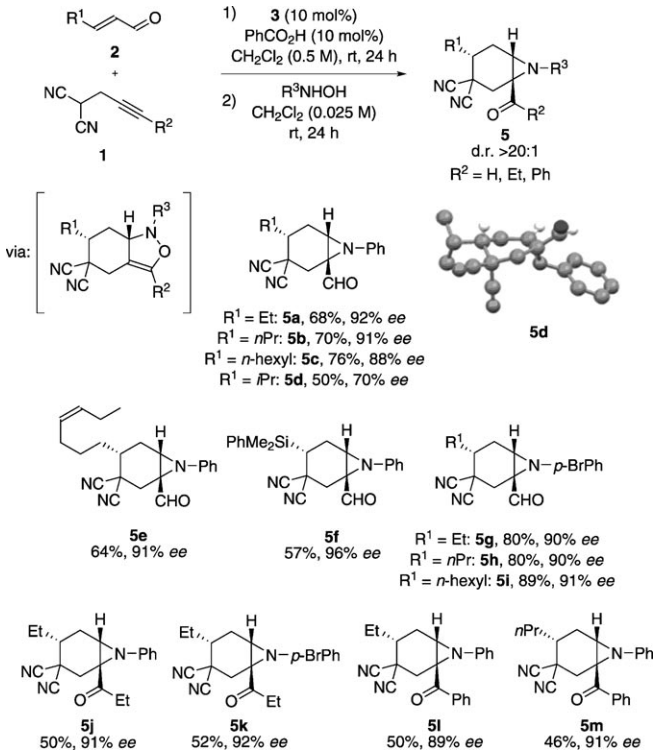
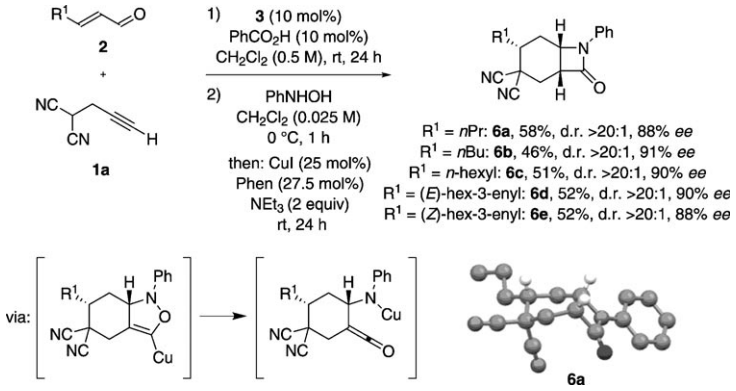
vided the Michael adduct **4**.[2a,f] Gratifyingly, subsequent dilution of the reaction mixture and addition of *N*-phenylhydroxylamine furnished the desired, bicyclic aziridine carbaldehyde **5a** in 68% yield and 92% *ee* as a single diastereoisomer. Encouraged by these findings, we turned our attention to the scope of the reaction (Scheme 2).



Scheme 2. Scope for the aziridine carbonyls **5** and crystal structure of **5d**.[9] For details see the Supporting Information.

In general, the developed reaction protocol proved to be broad with respect to the employed aldehyde **2**, forming the products as single diastereoisomers. A variety of aliphatic α,β-unsaturated aldehydes was successfully transformed into the corresponding aziridine carbaldehydes **5a**–**c** in high yields (68–76%) and high enantioselectivities (88–92% *ee*). Interestingly, branched α,β-unsaturated aldehyde **2d** resulted in diminished yield (50%) and enantioselectivity (70% *ee*) of **5d**. Nevertheless, the product gave crystals suitable for X-ray diffraction, unambiguously establishing the relative configuration of the products.[10,11] Aldehydes bearing functionalities in the side chain, such as an alkene or a dimethylphenylsilyl (DMPS) group, which might serve as a chemical handle for further transformations, could effectively be utilized, giving the corresponding products **5e** and **5f** in high yields (64 and 57%) and excellent enantioselectivities (91 and 96% *ee*). Notably, no undesired cycloaddition was observed in the case of the aldehyde substituted with an unsaturated side chain. Furthermore, *N*-(4-bromophenyl)hydroxylamine was successfully applied, affording the aziridine carbaldehydes **5g**–**i** in high yields (80–89%) and enantioselectivities (90–91% *ee*). Conducting the reaction with ethyl- or phenyl-substituted alkynes, provided the analogous aziridine ketones **5j**–**m** in good yields (46–52%), taking into account the multiple step reaction sequence involved, and in high enantioselectivities (89–92% *ee*), thereby significantly expanding the scope of the reaction.

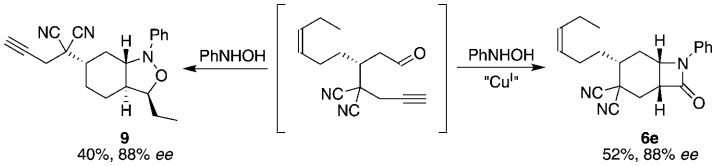
Next, we turned our attention to the synthesis of β-lactams, which should be accessible through a Cu^{I}-catalyzed reaction[12] from intermediate **4** (Scheme 3). Gratifyingly, in



Scheme 3. Scope for the synthesis of β-lactams **6** and crystal structure of **6a**.[9] For details see the Supporting Information.

the presence of 0.25 equivalents CuI, β-lactam **6a** was isolated in 58% yield and 88% *ee* from the reaction of hexen-2-al, malononitrile derivative **1a**, and *N*-phenylhydroxylamine. The relative configuration of **6a** was established by X-ray crystallography.[10,11] As a proof of concept, we investigated different aliphatic α,β-unsaturated aldehydes, which were successfully transformed into the corresponding β-lactams **6b** and **6c** in comparable good yields (46 and 51%) with excellent enantio- and diastereoselectivities (91 and 90% *ee*, d.r. > 20:1). Furthermore, unsaturated side chains were well tolerated, yielding **6d** and **6e** (52%, 90% *ee*, and 52%, 88% *ee*).

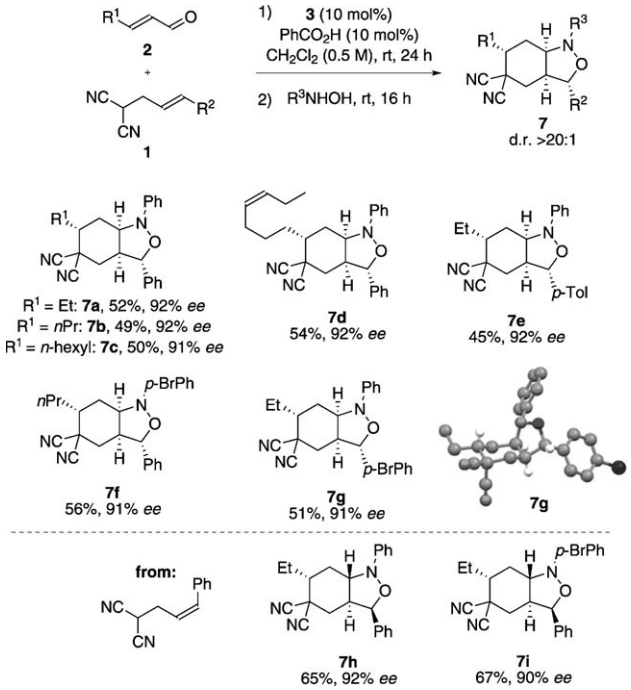
Surprisingly, in the formation of **6d**,**e**, no competing side reaction with the alkene moiety was observed, even though it is ideally positioned to form a six-membered ring and in general favored over the alkyne to act as acceptor in 1,3-dipolar cycloadditions. In the absence of copper, this reactivity is indeed observed, affording **9** (40%, 88% *ee*) as the major product (Scheme 4). This competition experiment clearly demonstrates the ability of copper to overrule the intrinsic reactivity of the system, allowing an effective tuning of the



Scheme 4. Competition experiments.

reaction outcome. The relative configuration of **9** was established by X-ray analysis.[10,11]

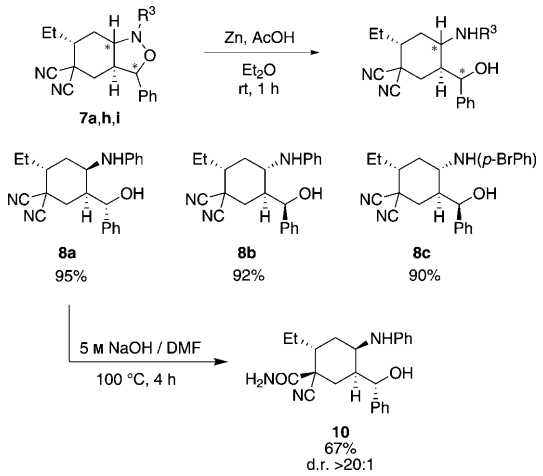
In contrast to the cycloaddition products of alkynes, the octahydrobenzo[*c*]isoxazoles **7** obtained by nitrone addition to alkenes are less strained and not prone to rearrangement. Importantly, **7** can be transformed into 1,3-amino alcohols after reductive cleavage of the N–O bond to give a straightforward access to this class of compounds. Therefore, alkene-tethered nucleophiles were investigated next (Scheme 5). Treating the in situ formed Michael adduct with



Scheme 5. Scope for the octahydrobenzo[*c*]isoxazoles **7** and crystal structure of **7g**. For details see the Supporting Information.

N-phenylhydroxylamine resulted in **7a** (52%, 92% *ee*) as a single *cis*-diastereoisomer formed via an *exo*-transition state. Fortunately, variation of the aldehyde was uncritical, as hexen-2-al and non-2-enal could successfully be employed, affording the corresponding products **7b** and **7c** in comparable yields (49 and 50%, respectively) and high enantioselectivities (92 and 91% *ee,* respectively). Moreover, alkenyl-substituted α,β-unsaturated aldehydes were well tolerated as demonstrated for **7d** (54%, 92% *ee*). Employment of either *N*-(4-bromophenyl)hydroxylamine or 4-bromo- and 4-methylphenyl-substituted nucleophiles was possible, yielding **7e–g** in 45–56% yield and high enantioselectivities (91–92% *ee*). X-ray diffraction unequivocally established the absolute configuration of **7g**.[11] Carrying out the reaction with a *Z*-alkene-substituted malononitrile should, due to the concerted nature of the cycloaddition, give access to diastereomeric octahydrobenzo[*c*]isoxazoles, thereby further enhancing the synthetic usefulness of the developed reaction cascade. As expected, the *exo* products were formed yielding the *trans*-configured bicycles **7h** and **7i** in 65% and 67% yield and enantioselectivities of 92% and 90% *ee*, respectively.

Unfortunately, neither **7h** nor **7i** gave crystals suitable for X-ray structure analysis. Nevertheless, careful analysis of 1D and 2D ^{1}H NMR spectra (see the Supporting Information), enabled the assignment of the relative configuration of **7h**.[10] As mentioned above, octahydrobenzo[*c*]isoxazoles **7** constitute direct precursors for 1,3-amino alcohols. Accordingly, to demonstrate the synthetic value of the reaction, reductive cleavage of the N–O bond was performed on selected substrates (Scheme 6). Compounds **7a**,**h**,**i** were reduced

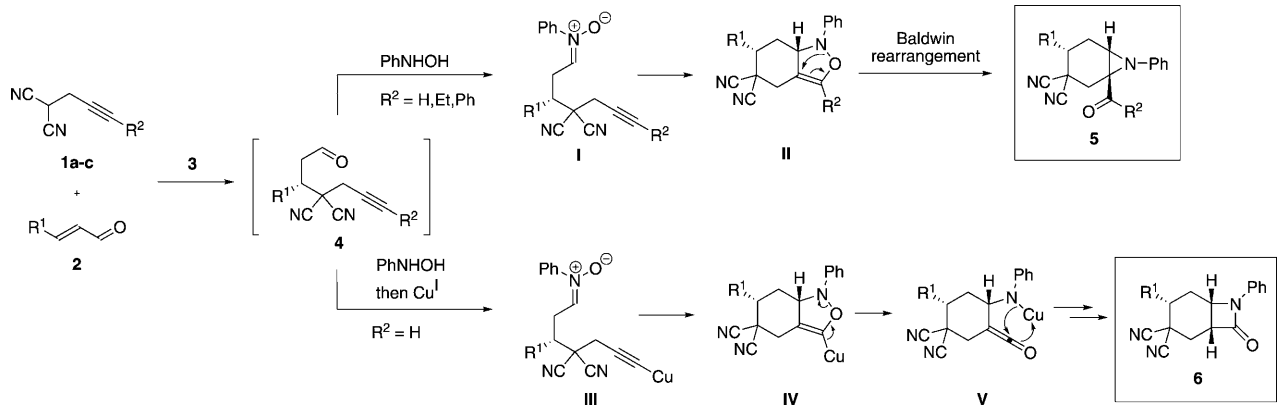


Scheme 6. Formation of 1,3-amino alcohols **8** by reductive N–O bond cleavage and selective hydrolysis to **10**. For details see the Supporting Information.

with zinc dust and acetic acid in diethyl ether to cleanly afford the corresponding 1,3-amino alcohols **8a–c** in excellent yields of 90–95%. To our delight, under basic, aqueous conditions selective hydrolysis of one of the geminal nitriles was achieved in good yield,[2a] thereby providing 1,3-amino alcohol **10** bearing a quaternary fifth stereocenter.

Scheme 7 summarizes the developed sequences leading to aziridine carbonyl compounds **5** and β-lactams **6**. Michael adduct **4** condenses with *N*-phenylhydroxylamine to form nitrone **I**. The latter undergoes intramolecular 1,3-dipolar cycloaddition with the alkyne moiety. Subsequently, spontaneous N–O bond cleavage of **II** and concomitant formation of **5**, known as the Baldwin rearrangement, occur (top, Scheme 7). In case of the Kinugasa reaction, copper acetylide nitrone **III** undergoes intramolecular 1,3-dipolar cycloaddition, forming vinyl cuprate **IV**. This collapses to ketene **V**, which, after aniline addition/tautomerization, affords β-lactams **6** (bottom, Scheme 7).

In conclusion, we have developed a highly divergent access to a variety of optically active three-, four-, and five-membered bicyclic N-heterocycles in good to high yields



Scheme 7. Mechanistic outline for the formation of aziridine carbonyls **5** and β-lactams **6**.

and excellent levels of stereocontrol. The one-pot approach relies on an organocatalytic conjugate addition/cycloaddition sequence. Baldwin rearrangement of transient hexahydrobenzo[*c*]isoxazoles affords aziridine carbonyls in high yields and stereoselectivities. In the presence of copper(I) salts, the sequence can be altered to yield β-lactams by the Kinugasa reaction from a common intermediate. Finally, an efficient asymmetric synthesis of octahydrobenzo[*c*]isoxazoles, their straightforward conversion into 1,3-amino alcohols, and the stereoselective hydrolysis of one of the nitrile functionalities were demonstrated.

Acknowledgements

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Keywords: 1,3-dipolar cycloaddition · N-heterocycles · one-pot reactions · organocatalysis

[1] Reviews on organocatalysis: a) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8; b) *Chem. Rev.* **2007**, *107*(12), special issue on organocatalysis; c) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; d) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; e) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178; f) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632; g) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2004**; h) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**.

[2] For selected examples, see: a) G. Dickmeiss, K. L. Jensen, D. Worgull, P. T. Franke, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *123*, 1618; *Angew. Chem. Int. Ed.* **2011**, *50*, 1580; b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; c) B. Westermann, M. Ayaz, S. S. van Berkel, *Angew. Chem.* **2010**, *122*, 858; *Angew. Chem. Int. Ed.* **2010**, *49*, 846; d) N. T. Jui, E. C. Y. Lee, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 10015; e) Ł. Albrecht, H. Jiang, G. Dickmeiss, B. Gschwend, S. G. Hansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 9188; f) K. L. Jensen, P. T. Franke, C. Arróniz, S. Kobbelgaard, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 1750; g) S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem.* **2009**, *121*, 9085; *Angew. Chem. Int. Ed.* **2009**, *48*, 8923; h) H. Jiang, N. Holub, M. W. Paixão, C. Tiberi, A. Falcicchio, K. A. Jørgensen, *Chem. Eur. J.* **2009**, *15*, 9638; i) C. Chandler, P. Galzerano, A. Michrowska, B. List, *Angew. Chem.* **2009**, *121*, 2012; *Angew. Chem. Int. Ed.* **2009**, *48*, 1978; j) G.-L. Zhao, R. Rios, J. Vesely, L. Eriksson, A. Córdova, *Angew. Chem.* **2008**, *120*, 8596; *Angew. Chem. Int. Ed.* **2008**, *47*, 8468; k) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; l) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, *46*, 467; m) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051.

[3] For recent examples, see: a) P. J. Chua, B. Tan, L. Yang, X. Zeng, D. Zhu, G. Zhong, *Chem. Commun.* **2010**, *46*, 7611; b) D. Zhu, M. Lu, L. Dai, G. Zhong, *Angew. Chem.* **2009**, *121*, 6205; *Angew. Chem. Int. Ed.* **2009**, *48*, 6089; c) J. Vesely, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2008**, *14*, 2693; for a systematic study, see: O. Tamura, N. Mita, T. Okabe, T. Yamaguchi, C. Fukushima, M. Yamashita, Y. Morita, N. Morita, H. Ishibashi, M. Sakamoto, *J. Org. Chem.* **2001**, *66*, 2602; for a review, see: K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863.

[4] For example: a) S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. De Sarlo, *Tetrahedron Lett.* **1990**, *31*, 3351; b) N. A. LeBel, N. Balasubramanian, *J. Am. Chem. Soc.* **1989**, *111*, 3363, and references therein.

[5] For pioneering work, see: a) V. A. Tartakovskii, O. A. Lukyanov, S. S. Novikov, *Russ. Chem. Bull.* **1966**, *15*, 2186; b) J. E. Baldwin, R. G. Pudussery, A. K. Qureshi, B. Sklarz, *J. Am. Chem. Soc.* **1968**, *90*, 5325; for a recent applications of this reaction, see: c) E. Gayon, O. Debleds, M. Nicouleau, F. Lamaty, A. van der Lee, E. Vrancken, J.-M. Campagne, *J. Org. Chem.* **2010**, *75*, 6050.

[6] For pioneering work, see: a) M. Kinugasa, S. Hashimoto, *J. Chem. Soc. Chem. Commun.* **1972**, 466; for recent applications of the Kinugasa reaction, see: b) R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082; c) X. Zhang, R. P. Hsung, H. Li, Y. Zhang, W. L. Johnson, *Org. Lett.* **2008**, *10*, 3477; d) S. Stecko, A. Mames, B. Furman, M. Chmielewski, *J. Org. Chem.* **2009**, *74*, 3094; for a highlight, see: J. Marco-Contelles, *Angew. Chem.* **2004**, *116*, 2248; *Angew. Chem. Int. Ed.* **2004**, *43*, 2198.

[7] For reviews, see: a) *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**; b) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437, and references therein.

[8] S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767.

[9] For reasons of a clearer presentation, the X-ray structure depicted is a mirror image of those deposited in the CCDC files (see Ref. [11]). Only the relative configuration was determined.

[10] We assume that the reaction products all possess the depicted absolute stereochemistry, as catalyst **3** has shown to generate (*R*)-configured stereocenters in conjugate additions of malononitriles to α,β-unsaturated aldehydes. See references [2a] and [2f] and X-ray structure of **7g**.
[11] See the Supporting Information for crystal structures. CCDC-806423 (**5d**) 809909 (**6a**) 806422 (**7g**) 807038 (**9**) contain the supplementary data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[12] Modified conditions to those previously reported were applied: M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999.

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