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Asymmetric Synthesis of Spirobenzazepinones with Atroposelectivity and Spiro-1,2-Diazepinones by NHC-Catalyzed [3+4] Annulation Reactions

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Abstract: *A strategy for the NHC-catalyzed asymmetric synthesis of spirobenzazepinones, spiro-1,2-diazepinones, and spiro-1,2-oxazepinones has been developed via [3+4]-cycloaddition reactions of isatin-derived enals (3C component) with in-situ-generated aza-o-quinone methides, azoalkenes, and nitrosoalkenes (4atom components). The [3+4] annulation strategy leads to the seven-membered target spiro heterocycles bearing an oxindole moiety in high yields and excellent enantioselectivities with a wide variety of substrates. Notably, the benzazepinone synthesis is atroposelective and an all-carbon spiro stereocenter is generated.*

The search for efficient approaches to synthesize nitrogen-containing heterocycles with biological activity starting from cheap and easily available substrates has always been a central goal in modern organic synthesis. In particular, seven-membered *N*-heterocycles are privileged structures that play an important role as pharmaceuticals in medicinal chemistry.[1] Typical examples with a benzazepine and a 1,2-diazepine scaffold are shown in Figure 1.[2] For instance, mozavaptan is used as a nonpeptide arginine vasopressin (AVP) V-2 receptor antagonist.[2c] It has been developed as a racemic mixture based on the central chirality of the stereocenter at C5. Later, it was shown that the *5S* enantiomer is the eutomer and the *5R* isomer the distomer.[2f] Interestingly, axial chirality is also present, and thus atropisomers with important pharmaceutical implications may exist.[2g] Although the atropisomers of mozavaptan could not be isolated separately, it was mentioned that the bioactivity is caused by the stereoisomer with *cis*,*aS*,*5S*-configuration.[2h,i] It is evident in this context that the development of efficient strategies for the catalytic asymmetric synthesis of such seven-membered N-heterocycles, including the aspects of atroposelectivity and the creation of spiro stereogenic centers, is highly desirable.

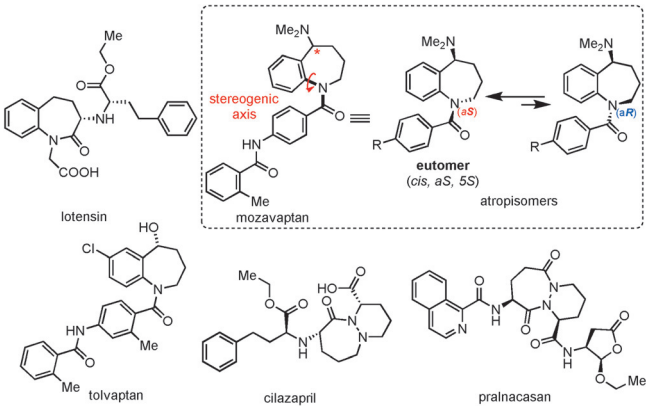

Figure 1. Examples of benzazepines and 1,2-diazepines.

Within the rapidly growing realm of organocatalysis, N-heterocyclic carbenes (NHCs) have emerged as a powerful tool in asymmetric synthesis, covering now a full subchapter of organocatalysis.[3] Among the various reactive intermediates available through NHC-Lewis-base catalysis, such as acyl anion,[4] enolate,[5] and homoenolate[6] equivalents, the latter ones play an especially important role in asymmetric annulation procedures. In particular, NHC-catalyzed [3+4] annulations via the homoenolate pathway turned out to be a reliable entry to seven-membered heterocycles.[6e–g] However, procedures for the direct asymmetric synthesis of seven-membered spiro-N-heterocycles via NHC-catalysis remain elusive because NHC-based homoenolate 3C components derived from simple enals cannot be used to create an all-carbon spiro-stereocenter (Scheme 1).

With this in mind, we wondered whether the combination of isatin-derived enals[7] and NHC-catalysis[8] together with aza-*o*-quinone methides or azoalkenes, which can be readily generated in situ from *N*-(*ortho*-chloromethyl)aryl amides[9] or α-halogeno hydrazones,[6g,10] respectively, can open a direct [3+4] annulation entry for the asymmetric synthesis of spirobenzazepinones and spiro-1,2-diazepinones bearing an oxindole moiety connected through the spirocenter. Herein, we report the first procedure for the NHC-catalyzed enantio- and atroposelective synthesis of the title spiro heterocycles.

The planned NHC-catalyzed [3+4] annulation reaction was evaluated by using the isatin-derived enal **1a** (1.1 equiv) and *N*-(*ortho*-chloromethyl)aryl amide **2a** (1.0 equiv) in dichloromethane (CH_2Cl_2) at room temperature. Notably, the reaction proceeded smoothly and afforded the desired

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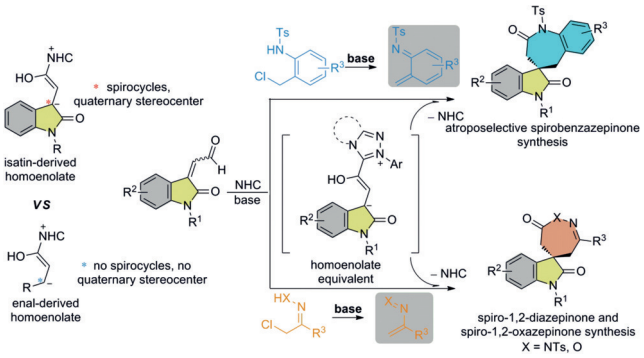
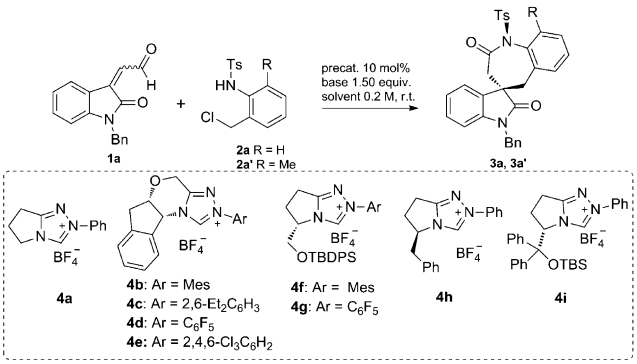


Scheme 1. Spirobenzazepine and spiro-1,2-diazepine synthesis by NHC catalysis.

product in moderate yield when the achiral triazolium salt **4a** as the precatalyst and K_3PO_4 as the base were used (Table 1, entry 1). Next, we examined enantiopure triazolium-derived NHC catalysts (entries 2–9). To our delight, we found that the precatalyst **4d** led to an efficient reaction (71%) with moderate diastereoselectivity (4:1) and a good enantiomeric ratio of 79:21 (entry 4). Switching from the precatalyst **4d** (*N*-perfluorobenzene) to **4e** (*N*-1,3,5-trichlorobenzene) led to no improvement in the enantiomeric ratio (entry 5). By screening different bases and solvents, Cs_2CO_3 and ethyl acetate were found to afford the desired product with improved e.r. (93:7), good yield, (68%) and moderate d.r. (4:1; entry 10). A further attempt to afford **3a**′ with excellent diastereoselectivity was carried out using **2a**′ as starting material (entry 11). However, slightly erosive effects on the reaction efficiency and selectivity (58%, 90:10 e.r.) were observed (for the complete optimization table, see the Supporting Information).

Our next step was to explore the generality of this approach to atropo- and enantioselectively assemble a range of substituted spirobenzazepinones bearing a quaternary stereocenter under the established optimal reaction conditions. As indicated in Table 2, a number of substituted isatin-derived enals **1** were found to be suitable for this reaction. Variations in the electronic (**3b–e**) and steric (**3f**) properties of the substituents on the benzene ring of the enals **1** were investigated and the corresponding spirobenzazepinones **3** were isolated in good yields with high enantiomeric ratios and good diastereoselectivities. For the purpose of product

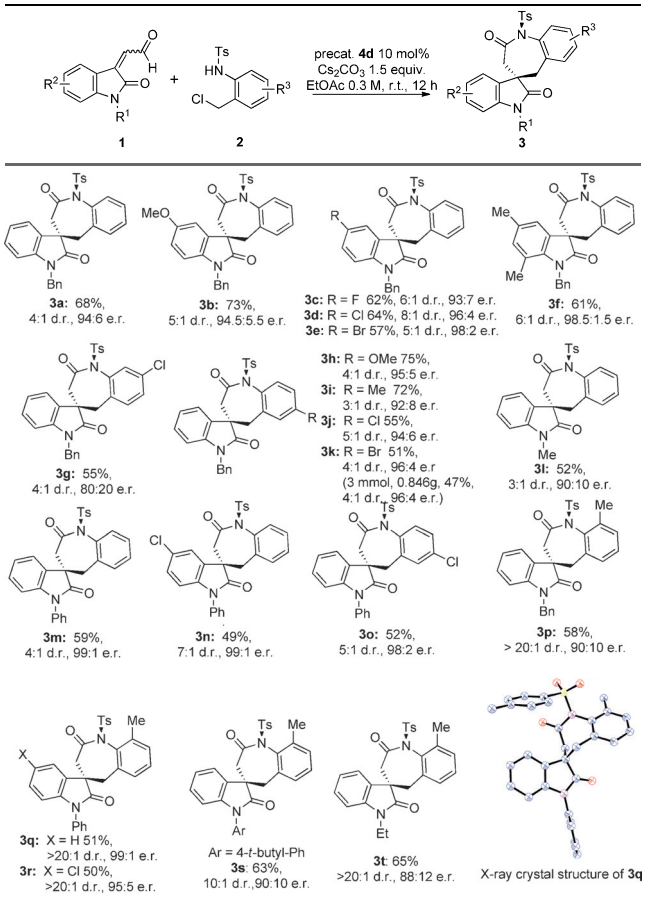
Table 1: Optimization of the NHC-catalyzed [3+4] annulation reactions.[a]



Entry	4	Solvent	Base	Yield [%][b]	d.r.[c]	e.r. [%][d]
1	**4a**	CH_2Cl_2	K_3PO_4	55	–	–
2	**4b**	CH_2Cl_2	K_3PO_4	58	4:1	72:28
3	**4c**	CH_2Cl_2	K_3PO_4	56	4:1	77:23
4	**4d**	CH_2Cl_2	K_3PO_4	71	5:1	79:21
5	**4e**	CH_2Cl_2	K_3PO_4	67	5:1	73:27
6	**4f**	CH_2Cl_2	K_3PO_4	55	3:1	62:38
7	**4g**	CH_2Cl_2	K_3PO_4	68	4:1	59:41
8	**4h**	CH_2Cl_2	K_3PO_4	63	4:1	74:26
9	**4i**	CH_2Cl_2	K_3PO_4	n.r.	–	–
10	**4d**	**EtOAc**	**Cs_2CO_3**	**68**	**4:1**	**93:7**
11[e]	**4d**	EtOAc	Cs_2CO_3	58	>20:1	90:10

[a] Reaction conditions: isatin-derived enal **1a** (0.22 mmol, 1.1 equiv) and **2a** (0.2 mmol, 1.0 equiv), 10 mol% catalyst, base (0.3 mmol, 1.5 equiv), solvent (1 mL), r.t., 12 h. [b] Yield of the isolated product **3** after chromatography. [c] The diastereomeric ratio of the atropisomers was determined by ^{1}H NMR analysis. [d] e.r. was determined by chiral HPLC analysis of the purified product. [e] **2a**′ was used as starting material. n.r. = No reaction.

Table 2: Atroposelective asymmetric synthesis of spirobenzazepinones.[a]



[a] Reaction conditions: isatin-derived enals **1** (0.33 mmol, 1.1 equiv), aryl sulfonamide **2** (0.3 mmol, 1.0 equiv), 10 mol% precatalyst **4d**, Cs_2CO_3 (0.45 mmol, 1.5 equiv), EtOAc (1.5 mL), r.t., 12 h; Yields of isolated products **3** after chromatography. The ratio of atropisomers (d.r.) was determined by ^{1}H NMR analysis. e.r. was determined by chiral HPLC analysis of the purified product.

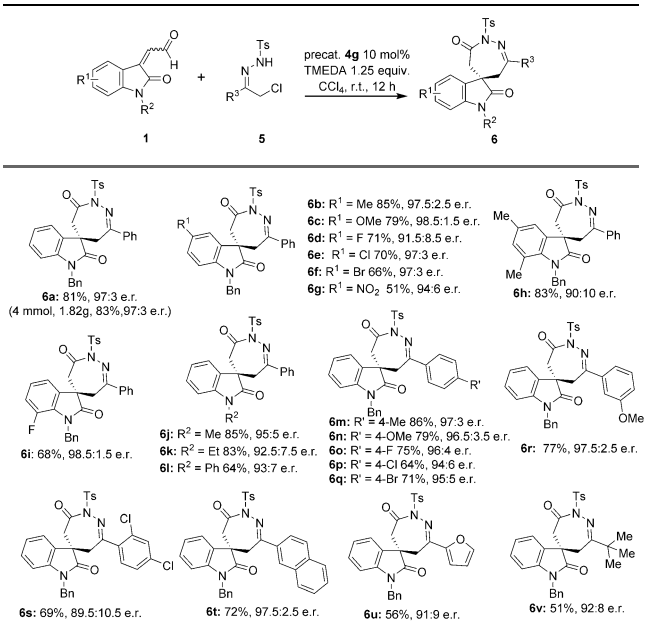
diversity, a wide range of *N*-(*ortho*-chloromethyl)aryl amides **2** was also examined. As shown in Table 2, a variety of electron-rich and electron-deficient substituents R^3 were compatible and afforded the expected spiroheterocycles (**3g–k**) in good yields, moderate diastereoselectivities, and high enantiomeric ratios. The exception was the 6-Cl-substituted amide **3g**, which resulted in reduced enantioselectivity. Furthermore, this NHC-catalyzed annulation reaction was extended by variation of the N-substituent R^1 of the enals **1**, resulting in good to excellent enantioselectivities (R = Me, Et, Ph, 4-*t*-BuPh). Research on atropisomerism[2d,11] has indicated that a substituent at the *ortho*-position of the benzene ring of seven-membered benzolactams increases the conformational barrier of the corresponding atropisomers. Thus, using *N*-(*ortho*-chloromethyl)aryl amides bearing a methyl group at the *ortho*-position (**2a′**), afforded excellent diastereoselectivities (**3p–t**). The absolute configuration given for all of the spirobenzazepinones **3**, with (*S*) at the spiro center and (a*S*) for the major atropisomer, is based on the X-ray structure analysis of **3q** (see Table 2 and the Supporting Information).[12]

To emphasize the generality of our approach, the applicability of the NHC-catalysis with isatin-derived enals **1** to generate spiro-1,2-diazepinones **6** was examined by using azoalkenes, which were obtained in situ from α-halogeno hydrazones **5** under basic conditions (Table 3). No coversion was observed under the previous standard conditions, whereas with CCl_4 as solvent, **4g** as precatalyst, and TMEDA as base, the corresponding spiro-1,2-diazepinone product **6a** was obtained in 81% yield with excellent enantioselectivity. The generality of this procedure in terms of various substrates was then explored. As indicated in Table 3, a broad range of different enal substrates bearing electron-neutral, -releasing, and -withdrawing substituents on the aromatic ring were investigated in the asymmetric annulation with *N*-tosyl hydrazone **5a**, giving the corresponding spiro-1,2-diazepinone products (**6a–i**) with excellent enantioselectivities and moderate to very good yields. Enal substrates with varied N-substituents (R_2 = Me, Et, Ph) could also be employed in this annulation procedure and led to excellent yields and high enantioselectivities (**6j–l**).

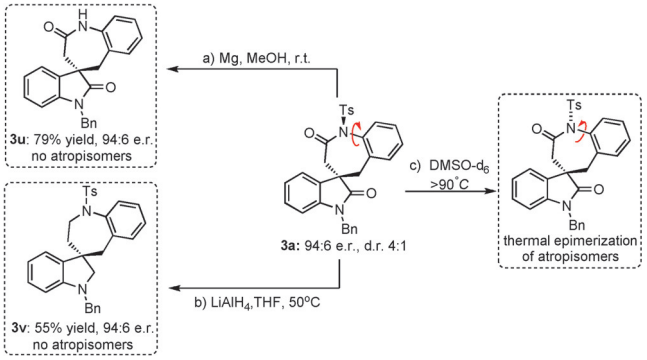
Various α-chloro *N*-tosyl hydrazones **5** were found to be suitable azoalkene precursors for this transformation, yielding the desired spiro-1,2-diazepinones **6** with excellent yields and high enantioselectivities in most cases (**6m–t**). Gratifyingly, the extension of the substrate range to heterocycle- or alkyl-substituted hydrazones **5u** and **v** was also successful and provided the related spiro [3+4] annulations products in very good enantioselectivities (**6u**, **v**). A gram-scale reaction using the current chiral NHC catalysis system worked well without affecting the efficiency and stereochemical outcome of the reaction.

Further investigations indicated that the atropisomerism caused by the high rotational barrier around the aryl–N bond in the spirobenzazepinone **3a** disappears by removing the *N*-tosyl group to form **3u** or by reducing the carbonyl group on the azepinone ring to give **3v**. Moreover, high-temperature ^{1}H-NMR experiments of **3a** in [D_6]DMSO were carried out indicating a coalescence and interconversion of the atropisomers at > 90 °C (Scheme 2; Supporting Information).

Table 3: Asymmetric synthesis of spiro-1,2-diazepinones.

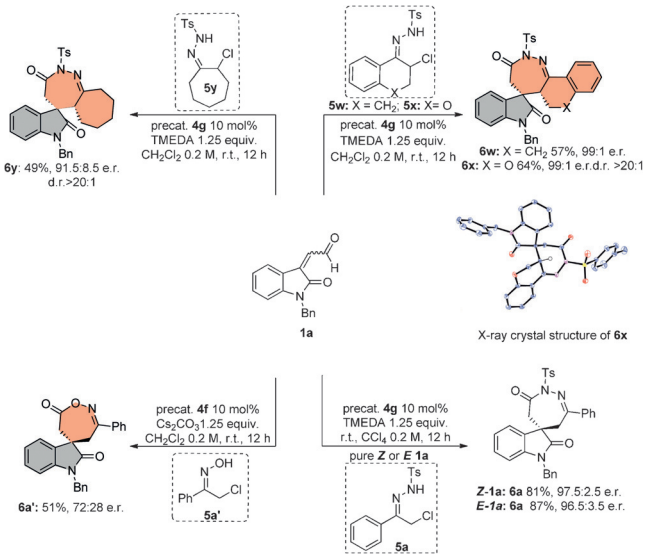


[a] Reaction conditions: isatin-derived enals **1** (0.33 mmol, 1.1 equiv), tosyl hydrazones **5** (0.3 mmol, 1.0 equiv), 10 mol% precatalyst **4g**, TMEDA (0.375 mmol, 1.25 equiv), CCl_4 (1.5 mL), r.t., 12 h; Yields of isolated products **6** after chromatography. e.r. was determined by chiral HPLC analysis of the purified product.

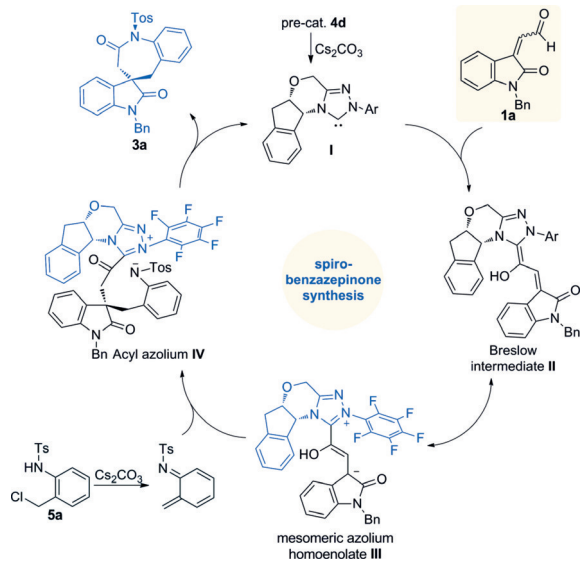


Scheme 2. Thermal epimerization and loss of atropisomerism study.

Additionally, polycyclic spiro-1,2-diazepinones could also be synthesized with the standard NHC catalysis system. When cyclic hydrazones **5w** and **5x** were used as reaction partners (Scheme 3), the polycyclic products **6w** and **6x** could be obtained in good yields and excellent diastereo- and enatioselectivities. Interestingly, when the seven-membered hydrazone **5y** was applied under the standard catalytic conditions, the corresponding polycyclic spiro-1,2-diazepinone **6y** with two fused seven-membered rings was obtained in 49% yield with an enantiomeric ratio of 91.5:8.5, which will greatly enrich the diversity of our method. An X-ray crystallographic analysis of compound **6x** was performed to determine the



Scheme 3. Polycyclic spiro-1,2-diazepinone and spiro-1,2-oxazepinone synthesis.



Scheme 4. Postulated mechanism for the asymmetric catalytic [3+4] annulation reactions.

absolute configuration of the spiro-1,2-diazepinone products (Scheme 3).[13] Further efforts were undertaken to synthesize spiro-1,2-oxazepinones using a similar NHC strategy employing α-chloro oximes **5a′** as substrates. Using the precatalyst **4f** together with Cs_2CO_3 as base and CH_2Cl_2 as solvent, the spiro-1,2-oxazepinone **6a′** could be obtained with good yield and a moderate enantiomeric ratio (72:28; Scheme 3). We then investigated the effect of the configuration of **1a** on the reaction with **5a**. Pure (*Z*)-**1a** and pure (*E*)-**1a** were freshly prepared according to literature procedures, respectively (see the Supporting Information), and were used as substrates for the asymmetric synthesis of **6a**. Under the standard conditions, the same product **6a** was obtained with only slightly different yield and enantioselectivity, which almost matched the result using a mixture of *Z*/*E*-**1a** as the starting material. These results indicate that the double bond configuration of **1a** has virtually no effect on this transformation in yield and enatioselectivity.

On the basis of the known NHC-catalyzed cycloaddition reactions, a possible mechanism for this asymmetric [3+4] annulation is shown in Scheme 4. The formation of spirobenzazepinone **3a** starts with the addition of the NHC **I** to the isatin-derived enal **1a** to generate the Breslow intermediates **II**, which in the mesomeric form represent the azolium homoenolate species **III**. From this intermediate the reaction proceeds via a conjugate addition to the in-situ-formed aza-*o*-quinone methide to create a new C–C bond and quaternary stereocenter. The resulting acyl azolium species **IV** then undergoes a lactamization to release the NHC catalyst and furnish the spirobenzazepinone **3a** with atroposelectivity. A similar catalytic pathway is postulated for the synthesis of the spiro-1,2-diazepinones **6**.

In conclusion, we have developed an asymmetric, NHC-catalyzed formal [3+4] cycloaddition of isatin-derived enals with in-situ-formed aza-*o*-quinone methides and azoalkenes or nitrosoalkenes to synthesize a series of spirobenzazepinones and spiro-1,2-diazepinone heterocycles, as well as spiro-1,2-oxazepinones, in good yields with very good to excellent enantioselectivities. Notably, the asymmetric NHC-catalyzed annulation strategy described here allows the atroposelective asymmetric synthesis of the spirobenzazepinones and also represents a new approach to access these pharmaceutically important heterocycles bearing a quaternary all-carbon stereocenter in gram amounts. Further applications of NHC-catalysis for the synthesis of related heterocycles will be reported in due course.

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Keywords: 1,2-diazepinone · asymmetric synthesis · benzazepinone · N-heterocyclic carbene · spiro compound

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[1] a) J. H. Ryan, C. Hyland, A. G. Meyer, J. A. Smith, J. X. Yin, *Prog. Heterocycl. Chem.* **2012**, *24*, 493–536; b) J. J. Vaquero, A. M. Cuadro, B. Herradón in *Modern Heterocyclic Chemistry*, *Vol. 4* (Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga), Wiley-VCH, Weinheim, **2011**; c) D. Lednicer, *Strategies for Organic Drug Synthesis and Design*, Wiley, New York, Chap. 12, **1998**, pp. 362–378.

[2] a) J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz, B. M. Finn, *J. Med. Chem.* **1985**, *28*, 1511–1516; b) M. R. Attwood, C. H. Hassall, A. Krohn, G. Lawton, S. Redshaw, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1011–1019; c) H. Ogawa, H. Yamashita, K. Kondo, Y. Yamamura, H. Miyamoto, K. Kan, K. Kitano, M. Tanaka, K. Nakaya, S. Nakamura, T. Mori, M. Tominaga, Y. Yabuuchi, *J. Med. Chem.* **1996**, *39*, 3547–3555; d) A. L. C. Robidoux, J. D. Wilson, P. Dieterich, N. Storer, S. Leonardi,

(Vertex Pharmaceuticals Incorporated, U.S.), US 6559304 B1, **2003**; e) A. Cordero-Vargas, B. Quiclet-Sire, S. Z. Zard, *Bioorg. Med. Chem.* **2006**, *14*, 6165 – 6173; f) H. Tabata, J. Nakagomi, D. Morizono, T. Oshitari, H. Takahashi, H. Natsugari, *Angew. Chem. Int. Ed.* **2011**, *50*, 3075 – 3079; *Angew. Chem.* **2011**, *123*, 3131 – 3135; g) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPante, *Angew. Chem. Int. Ed.* **2009**, *48*, 6398 – 6401; *Angew. Chem.* **2009**, *121*, 6516 – 6520; h) T. Yoneda, H. Tabata, J. Nakagomi, T. Tasaka, T. Oshitari, H. Takahashi, H. Natsugari, *J. Org. Chem.* **2014**, *79*, 5717 – 5727; For a revision, see: i) H. Tabata, T. Yoneda, T. Tasaka, S. Ito, T. Oshitari, H. Takahashi, H. Natsugari, *J. Org. Chem.* **2016**, *81*, 3136 – 3148.

[3] For reviews on NHC catalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606 – 5655; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000; *Angew. Chem.* **2007**, *119*, 3046 – 3058; c) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182 – 1195; d) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336 – 5346; e) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; f) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314 – 325; *Angew. Chem.* **2012**, *124*, 320 – 332; g) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, ***44***, 2295 – 2309; h) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 11686 – 11698; *Angew. Chem.* **2012**, *124*, 11854 – 11866; i) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617 – 1639; j) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906 – 4917; k) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664 – 4678; l) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696 – 707; m) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307 – 9387; n) S. R. Yetra, A. Patra, A. T. Biju, *Synthesis* **2015**, *47*, 1357 – 1378.

[4] a) H. U. Vora, T. Rovis, *Aldrichimica Acta* **2011**, *44*, 3 – 11; b) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 10402 – 10405; c) X. Q. Fang, X. K. Chen, H. Lv, Y. R. Chi, *Angew. Chem. Int. Ed.* **2011**, *50*, 11782 – 11785; *Angew. Chem.* **2011**, *123*, 11986 – 11989; d) J. J. Cheng, Z. J. Huang, Y. G. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592 – 8596; *Angew. Chem.* **2013**, *125*, 8754 – 8758; e) A. Ungureanu, A. Levens, L. Candish, D. W. Lupton, *Angew. Chem. Int. Ed.* **2015**, *54*, 11780 – 11784; *Angew. Chem.* **2015**, *127*, 11946 – 11950.

[5] a) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406 – 16407; b) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418 – 8420; c) J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20661 – 20665; d) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295 – 2309; e) E. O. McCusker, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2013**, *52*, 13616 – 13620; *Angew. Chem.* **2013**, *125*, 13861 – 13865; f) V. R. Yatham, J. M. Neudörfl, N. E. Schlörer, A. T. Berkessel, *Chem. Sci.* **2015**, *6*, 3706 – 3711; g) X. Q. Dong, W. Yang, W. M. Hu, J. W. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 660 – 663; *Angew. Chem.* **2015**, *127*, 670 – 673.

[6] a) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205 – 6208; *Angew. Chem.* **2004**, *116*, 6331 – 6334; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370 – 14371; c) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766 – 771; d) Z. Q. Fu, J. Xu, T. S. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835 – 839; e) J. Izquierdo, A. Orue, K. A. Scheidt, *J. Am. Chem. Soc.* **2013**, *135*, 10634 – 10637; f) H. Lv, W. Q. Jia, L. H. Sun, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 8607 – 8610; *Angew. Chem.* **2013**, *125*, 8769 – 8772; g) C. Guo, B. Sahoo, C. G. Daniliuc, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17402 – 17405; h) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040 – 5052; i) T. Shu, Q. J. Ni, X. X. Song, K. Zhao, T. Y. Wu, R. Puttreddy, K. Rissanen, D. Enders, *Chem. Commun.* **2016**, *52*, 2609 – 2611.

[7] a) R. Liu, J. Zhang, *Chem. Eur. J.* **2013**, *19*, 7319 – 7323; b) R. Liu, J. Zhang, *Org. Lett.* **2013**, *15*, 2266 – 2269; c) T. Mukaiyama, K. Ogata, I. Sato, Y. Hayashi, *Chem. Eur. J.* **2014**, *20*, 13583 – 13588; d) T. Mukaiyama, K. Ogata, T. Ono, Y. Hayashi, *ChemCatChem* **2015**, *7*, 155 – 159.

[8] a) D. Xie, L. Yang, Y. Lin, Z. Zhang, D. Chen, X. Zeng, G. Zhang, *Org. Lett.* **2015**, *17*, 2318 – 2321; b) J. Xu, W. Zhang, Y. Liu, S. Zhu, M. Liu, X. Hua, S. Chen, T. Lu, D. Du, *RSC Adv.* **2016**, *6*, 18601 – 18606.

[9] a) H. Steinhagen, E. J. Corey, *Angew. Chem. Int. Ed.* **1999**, *38*, 1928 – 1931; *Angew. Chem.* **1999**, *111*, 2054 – 2056; b) F. Avemaria, S. Vanderheiden, S. Bräse, *Tetrahedron* **2003**, *59*, 6785 – 6796; c) Q. Q. Yang, C. Xiao, L. Q. Lu, J. An, F. Tan, B. J. Li, W. J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 9137 – 9140; *Angew. Chem.* **2012**, *124*, 9271 – 9274; d) Q. Q. Yang, Q. Wang, J. An, J. R. Chen, L. Q. Lu, W. J. Xiao, *Chem. Eur. J.* **2013**, *19*, 8401 – 8404; e) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 10589 – 10592; f) M. T. Hovey, C. T. Check, A. F. Sipher, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2014**, *53*, 9603 – 9607; *Angew. Chem.* **2014**, *126*, 9757 – 9761; g) G. Zhan, M. L. Shi, Q. He, W. Du, Y. C. Chen, *Org. Lett.* **2015**, *17*, 4750 – 4753; h) H. M. Liao, A. Chatupheeraphat, C. C. Hsiao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 15540 – 15544; *Angew. Chem.* **2015**, *127*, 15760 – 15765; i) J. Y. Liu, H. Lu, C. G. Li, Y. M. Liang, P. F. Xu, *Synlett* **2016**, *27*, 1287 – 1291.

[10] a) C. B. Reese, H. P. Sanders, *J. Chem. Soc. Perkin Trans. 1* **1982**, 2719 – 2724; b) O. A. Attanasi, L. De Crescentini, G. Favi, P. Filippone, F. Mantellini, F. R. Perrulli, S. Santeusanio, *Eur. J. Org. Chem.* **2009**, 3109 – 3127; c) J. M. Hatcher, D. M. Coltart, *J. Am. Chem. Soc.* **2010**, *132*, 4546 – 4547; d) J. R. Chen, W. R. Dong, M. Candy, F. F. Pan, M. Jörres, C. Bolm, *J. Am. Chem. Soc.* **2012**, *134*, 6924 – 6927.

[11] a) H. Tabata, K. Akiba, S. Lee, H. Takahashi, H. Natsugari, *Org. Lett.* **2008**, *10*, 4871 – 4874; b) H. Tabata, N. Wada, Y. Takada, T. Oshitari, H. Takahashi, H. Natsugari, *J. Org. Chem.* **2011**, *76*, 5123 – 5131; c) H. Tabata, T. Yoneda, T. Oshitari, H. Takahashi, H. Natsugari, *J. Org. Chem.* **2013**, *78*, 6264 – 6270; d) T. Yoneda, H. Tabata, T. Tasaka, T. Oshitari, H. Takahashi, H. Natsugari, *J. Med. Chem.* **2015**, *58*, 3268 – 3273.

[12] CCDC 1453056 (**3q**) contains the supplementary crystallographic 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.

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