Published in final edited form as:

Angew Chem Int Ed Engl. 2019 April 23; 58(18): 5941–5945. doi:10.1002/anie.201900600.

Carbene-Catalyzed Enantioselective Decarboxylative Annulations to Access Dihydrobenzoxazinones and Quinolones

Ansoo Lee,

Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208 (USA)

Joshua L. Zhu,

Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208 (USA)

Taisiia Feoktistova,

Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, OR 97331 (USA)

Alexander C. Brueckner,

Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, OR 97331 (USA)

Paul H.-Y. Cheong^{*}, and

Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, OR 97331 (USA)

Karl A. Scheidt^{*}

Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208 (USA)

Abstract

A direct decarboxylative strategy for the generation of aza-o-quinone methides (aza-o-QMs) by *N*-heterocyclic carbene (NHC) catalysis has been discovered and explored. This process requires no stoichiometric additives in contrast with current approaches. Aza-o-QMs react with trifluoromethyl ketones via a formal [4+2] manifold to access highly enantioenriched dihydrobenzoxazin-4-one products, which can be converted to dihydroquinolones via an interesting stereoretentive aza-Petasis-Ferrier rearrangement sequence. Complementary dispersion-corrected density functional theory (DFT) studies provided an accurate prediction of the reaction enantioselectivity, and lend further insight to the origins of stereocontrol. Additionally, a computed potential energy surface around the major transition structure suggests a concerted asynchronous mechanism for the formal annulation.

Graphical Abstract

^{*}Corresponding Authors scheidt@northwestern.edu; cheongh@oregonstate.edu.

Supporting information for this article is given via a link at the end of the document.

A direct decarboxylative strategy for the generation of aza-o-quinone methides (aza-o-QMs) by *N*-heterocyclic carbene (NHC) catalysis has been discovered and explored. Aza-o-QMs react with trifluoromethyl ketones via a formal [4+2] manifold to access highly enantioenriched dihydrobenzoxazin-4-one products. Complementary dispersion-corrected DFT studies provided insight to the origins of stereocontrol and suggested a concerted asynchronous mechanism for the formal

Keywords

annulation; asymmetric synthesis; *N*-heterocyclic carbene; organocatalysis; homogeneous catalysis

Dihydrobenzoxazinones are an important class of *N*-heterocyclic compounds widely found in pharmaceutical molecules and natural products.^[1] The dihydrobenzoxazinone structural motif is also commonly used as an intermediate for the construction of many other heterocyclic compounds.^[2] Consequently, new synthetic methods for the preparation of enantioenriched dihydrobenzoxazinones could fuel further studies on this versatile compound class. To date, the majority of asymmetric methods for dihydrobenzoxazinone synthesis has focused on the dihydrobenzoxazin-2-one substructure, using a variety of methods including formal [4+2] cycloaddition of o-benzoquinone imides with ketenes,^[3] Rh-catalyzed conjugate addition,^[4] Ir-catalyzed hydrogenation,^[5] and Brønsted acid-catalyzed transfer hydrogenation.^[6] The isomeric dihydrobenzoxazin-4-one substructure is also prevalent in both natural products and drug candidates. Although several straightforward racemic syntheses of dihydrobenzoxazin-4-ones have been reported, enantioselective methods for their construction remain underdeveloped to date.^[7]

N-heterocyclic carbene (NHC) catalysis has emerged as a powerful strategy for the construction of carbo- and heterocyclic compounds over the past decade.^[8] NHC-catalyzed Umpolung reactions employing enals has provided access to numerous divergent nucleophilic species, including acyl anion, enolate, and homoenolate equivalents. In 2011, Ye demonstrated that NHC catalysis could also access dienolate equivalents.^[9] Following Ye's preliminary disclosure, several reports of reactions employing "azolium dienolates" generated from various carbonyl precursors have emerged.^[10] Particularly, the NHC-catalyzed γ -functionalization of aromatic substrates^[11] has received attention due to the innovative deployment of unconventional o-quinodimethanes (o-QDMs) as substrates (Scheme 1a).^[12]

In 2013, Chi and co-workers initially reported NHC-bound o-QDM intermediates could be generated from o-methyl heteroaryl aldehydes^[11a] and o-methyl heteroaryl esters.^[11b]

Following these studies, several approaches to extend this reactivity to carbocyclic aromatic systems have emerged, notably, Glorius^[11c] and Rovis^[11d] found that NHCs could displace an appropriate benzylic leaving group to access the corresponding NHC-bound o-QDMs (Scheme 1a). There have been significantly fewer developments employing o-quinone methides (o-QMs) or aza-o-quinone methides (aza-o-QMs) as nucleophiles in NHC catalysis. A notable recent advance by Chi employed salicylaldehydes in the presence of stoichiometric oxidant and base to generate an NHC-bound o-QM, which participated in an annulation with trifluoromethyl ketone electrophiles (Scheme 1b).^[13] These contributions have expanded the scope of carbene catalysis, while simultaneously presenting opportunities to develop new and complementary methods employing NHC-bound o-QDM-like nucleophiles. Herein, we report a decarboxylative transformation proceeding via an NHC-bound aza-o-QM intermediate to access enantioenriched dihydrobenzoxazin-4-ones (Scheme 1c). This advance generates CO₂ as the byproduct and does not require external oxidants or stoichiometric bases, and represents the first use of NHC-bound aza-o-QMs as nucleophilic partners in asymmetric catalysis.

We initiated our studies on the decarboxylative cycloaddition using *N*-methylisatoic anhydride substrate **1a** with trifluoromethyl ketone **2a** (Scheme 2). An achiral triazolium catalyst with the strong, and non-nucleophilic base KHMDS provided the desired dihydrobenzoxazinone **3a** in moderate isolated yield at 30 °C (see SI). After evaluating triazolium catalysts **A–D**, we found that catalyst **D** bearing a mesityl substituent gave the product **3a** in 19% yield and 98:2 er, while less nucleophilic NHCs (**B** and **C**) did not provide desired reactivity with **1a**.^[15] We thus investigated the reaction using catalyst **E**^[16] and obtained **3a** in 72% yield and 97:3 er at 50 °C. With the optimal catalyst system identified, we moved to explore the reaction scope of these new NHC-catalyzed decarboxylative cycloadditions.

A survey of different *N*-methyl isatoic anhydrides and trifluoromethyl ketones is summarized in Table 1. Trifluoromethyl ketones (**2**) with para and meta substituents of varying electronic and steric parameters were all suitable substrates for the reaction. Ketones **2a–h** reacted with **1a** in the presence of catalyst **E** generating the desired products **3b–h** in moderate to good yields (49–91%) and with high stereoselectivity in all cases (95:5–98:2 er). The reactions of 3,5-substituted ketones also provided the desired products **3i** and **3j** in moderate yields and high stereoselectivity (56%, 97:3 er and 77%, 95:5 er, respectively). We next investigated the reaction scope of a variety of isatoic anhydrides (**1**). The reactions of anhydride substrates possessing electron-withdrawing halogen substituents provided products **3l–p** with good yields (66–78%) and high stereoselectivity (95:5–96:4 er), although we found that for these substrates reducing the reaction temperature to 35 °C was necessary to observe high stereoselectivity. When anhydrides with electron-donating substituents such as methyl and methoxy groups were reacted with the trifluoromethyl ketone **2a**, products **3q–s** were also obtained in moderate to good yields (47–80%) and high stereoselectivity (96:4–97:3 er). Reactions attempted using ortho-substituted aryl trifluoromethyl ketones,^[17] alkyl-trifluoromethyl ketones,^[18] or α -keto esters gave the desired products with diminished yields, whereas isatins did not react under the current conditions (Table 1, bottom, and SI).

In addition, different N-substituted isatoic anhydrides showed poor reactivity under current conditions (see the SI).

Potential catalytic pathways for the annulation are summarized in Scheme 3. The addition of catalyst **E** to anhydride **1a** and subsequent release of CO₂ generates NHC-bound aza-o-QM intermediate **I**. Notably, we observed a mass correlating to intermediate **I** by high-resolution mass spectrometry (see SI), which was somewhat surprising as aza-o-QMs are perceived to be highly reactive and transient species.^[19] This key intermediate **I** can undergo a concerted [4+2] pathway or a stepwise Michael addition/acylation. In the [4+2] pathway, concerted addition of trifluoromethyl ketone **2** and the intermediate **I** via **II** affords the product **3**. In the Michael addition/acylation pathway, a carbon-nitrogen bond is formed via **III** to generate intermediate **IV**, which undergoes O-acylation to regenerate the NHC **E**.

To first gain insight into the origins of stereocontrol, we analyzed the cycloaddition transition structures involving catalyst **E**, anhydride **1a** and trifluoromethyl ketone **2a** with the ω B97XD/6–31G(d)/SMD(Toluene) level of theory at 323 K to match experimental conditions (Figure 1).^[20] The transition structure (TS) leading to the (*S*)-product ((*S*)-**II**) was predicted to be 3.5 kcal/mol more stable than that leading to the (*R*)-product ((*R*)-**II**). *After these predictions were made*, experiments indeed validated these predictions (%ee = 94; $G_{\text{exp}}^{\ddagger} = 2.2$ kcal/mol).

Distortion-interaction analyses of the two TSs were performed to elucidate the origins of selectivity (see the SI).^[21] Gas-phase electronic energies of the TS fragments were compared to their corresponding ground-state structures.^[22] Three important observations resulted: (1) The NHC-bound aza-o-QM complexes in both TSs were similarly distorted ($E = 1.0$ kcal/mol). (2) The trifluoromethyl ketone in the **Major-TS**, (*S*)-**II** was also similarly distorted compared to the **Minor-TS**, (*R*)-**II** by 1.8 kcal/mol. (3) Most importantly, the **Major-TS**, (*S*)-**II** was significantly more stabilized by the interaction energy than the **Minor-TS**, (*R*)-**II** (–33.6 kcal/mol versus –27.9 kcal/mol, respectively). We hypothesize this drastic difference in stabilizing interaction energy is due to a more favorable electrostatic interaction in the **Major-TS**, (*S*)-**II** over the **Minor-TS**, (*R*)-**II**. In (*S*)-**II**, the positively charged NHC-bound o-QM is stabilized by close proximity to the CF₃–group, bearing a partial negative charge. In contrast, (*R*)-**II** exhibits a relatively weak C–H $\cdots\pi$ interaction between the trifluoromethyl ketone phenyl group and the positively charged NHC complex (Figure 1, green lines).

To better understand if the NHC-catalyzed annulation was concerted or stepwise (Scheme 3), we next computed the potential energy surface around the **Major-TS**, (*S*)-**II** (see Figure 2). The energies were computed by fixing the distance between the nucleophilic nitrogen of the NHC-bound o-QM and the electrophilic carbon of trifluoromethyl ketone **2a** (C–N bond) and varying distances corresponding to the second forming σ -bond. The surface shows that only one saddle point exists, suggesting a concerted process with no intervening intermediates.^[23]

Finally, the utility of these new enantioenriched dihydrobenzoxazinone products was explored (Scheme 4). The methylenation of **3a** or **3n** using the Tebbe reagent provided vinyl

ether derivatives (**4**). A subsequent aza-Petasis-Ferrier rearrangement^[24] gave the corresponding dihydroquinolone **5** with *retention* of chirality as determined by X-ray crystallography. This unprecedented sequence involving memory of chirality^[25] presumably involves a Lewis acid-promoted ring opening to generate initially a single atropisomer of the Me₂AlCl-enolate intermediate (**A1**) from **4**. The interconversion of this iminium enolate to atropisomer **A2** is apparently slow relative to a rapid intramolecular Mannich reaction affording dihydroquinolones (**5**) with a CF₃-group at the C2 position. Trifluoromethyl groups are common in pharmaceutical molecules to improve metabolic stability, lipophilicity and permeability.^[26] Therefore, we anticipate that these enantioenriched heterocycles with a CF₃-bearing stereocenter can be leveraged to explore new bioactive dihydroquinolone scaffolds.^[27]

An efficient asymmetric formal [4+2] cycloaddition of isatoic anhydride with trifluoromethyl ketones through NHC-mediated decarboxylative catalysis has been developed. This process generates an NHC-bound aza-o-QM as a key intermediate through liberation of carbon dioxide and avoids stoichiometric additives. Computations elucidated the origins of stereocontrol and revealed the concerted nature of the [4+2] process. This approach represents a highly versatile and selective transformation to provide enantioenriched dihydrobenzoxazin-4-ones with a CF₃-bearing stereocenter. Investigations involving these new NHC-bound intermediates and a variety of electrophile classes are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Financial support for this work has been provided by NIGMS R01 GM073072. PHYC gratefully acknowledges financial support from the Bert and Emelyn Christensen and Vicki & Patrick F. Stone families. PHYC, ACB, and TF acknowledge the National Science Foundation (NSF, CHE-1352663). The authors thank Keegan Fitzpatrick (NU) for X-ray crystallographic assistance and Ada Kwong (NU) for assistance with mass spectrometry.

References

- [1]. For selected reviews, see: a) Powers JC, Asgian JL, Ekici ÖD, James KE, Chem. Rev. 2002, 102, 4639–4750 [PubMed: 12475205] b) Ilaš J, Anderluh PŠ, Dolenc MS, Kikelj D, Tetrahedron 2005, 61, 7325–7348 c) Macías FA, Marín D, Oliveros-Bastidas A, Molinillo JMG, Nat. Prod. Rep. 2009, 26, 478–489. [PubMed: 19642418]
- [2]. Coppola GM, Heterocyclic J. Chem 1999, 36, 563–588.
- [3]. Wolfer J, Bekele T, Abraham CJ, Dogo-Isonagie C, Lectka T, Angew. Chem. Int. Ed. 2006, 45, 7398–7400.
- [4]. Zhang X, Xu B, Xu M-H, Org. Chem. Front. 2016, 3, 944–948.
- [5]. Núñez-Rico JL, Vidal-Ferran A, Org. Lett. 2013, 15, 2066–2069. [PubMed: 23573959]
- [6]. a) Rueping M, Antonchick AP, Theissmann T, Angew. Chem. Int. Ed. 2006, 45, 6751–6755 b) Lu L-Q, Li Y, Jung K, Beller M, J. Am. Chem. Soc. 2015, 137, 2763–2768. [PubMed: 25587941]
- [7]. For selected examples on the synthesis of dihydrobenzoxazin-4-ones, see: a) Wang X, Gallardo-Donaire J, Martin R, Angew. Chem. Int. Ed. 2014, 53, 11084–11087 b) Zhang N, Cheng R, Zhang-Negrerie D, Du Y, Zhao K, J. Org. Chem. 2014, 79, 10581–10587 [PubMed: 25279661] c) Patel K, Deshmukh SS, Bodkhe D, Mane M, Vanka K, Shinde D, Rajamohanan PR, Nandi S,

Vaidhyanathan R, Chikkali SH, J. Org. Chem. 2017, 82, 4342–4351 [PubMed: 28378576] d) Qi X, Li R, Li HP, Peng JB, Ying J, Wu XF, ChemCatChem 2018, 10, 3415–3418e) Kumar P, Gupta M, Bahadur V, Parmar VS, Singh BK, Eur. J. Org. Chem. 2018, 2018, 1552–1558.

- [8]. For reviews on NHC catalysis, see: a) Enders D, Niemeier O, Henseler A, Chem. Rev. 2007, 107, 5606–5655 [PubMed: 17956132] b) Bugaut X, Glorius F, Chem. Soc. Rev. 2012, 41, 3511–3522 [PubMed: 22377957] c) Vora HU, Wheeler P, Rovis T, Adv. Synth. Catal. 2012, 354, 1617–1639 [PubMed: 23538785] d) Izquierdo J, Hutson GE, Cohen DT, Scheidt KA, Angew. Chem. Int. Ed. 2012, 51, 11686–11698e) Cohen DT, Scheidt KA, Chem. Sci. 2012, 3, 53–57 [PubMed: 26413259] f) Mahatthananchai J, Bode JW, Acc. Chem. Res. 2014, 47, 696–707 [PubMed: 24410291] g) Hopkinson MN, Richter C, Schedler M, Glorius F, Nature 2014, 510, 485 [PubMed: 24965649] h) Menon RS, Biju AT, Nair V, Chem. Soc. Rev. 2015, 44, 5040–5052 [PubMed: 26014054] i) Flanigan DM, Romanov-Michailidis F, White NA, Rovis T, Chem. Rev. 2015, 115, 9307–9387 [PubMed: 25992594] j) Wang MH, Scheidt KA, Angew. Chem. Int. Ed. 2016, 55, 14912–14922.
- [9]. Shen LT, Shao PL, Ye S, Adv. Synth. Catal. 2011, 353, 1943–1948.
- [10]. For a recent review on the transformations via azolium dienolate, see: Chen XY, Liu Q, Chauhan P, Enders D, Angew. Chem. Int. Ed. 2018, 57, 3862–3873.
- [11]. a) Chen X, Yang S, Song BA, Chi YR, Angew. Chem. Int. Ed. 2013, 52, 11134–11137b) Xu J, Yuan S, Miao M, Org. Lett. 2016, 18, 3822–3825 [PubMed: 27391039] c) Janssen-Müller D, Singha S, Olyschläger T, Daniliuc CG, Glorius F, Org. Lett. 2016, 18, 4444–4447 [PubMed: 27549614] d) Chen D-F, Rovis T, Synthesis 2017, 49, 293–298 [PubMed: 28690345] e) Cheng J, Sun J, Yan J, Yang S, Zheng P, Jin Z, Chi YR, J. Org. Chem. 2017, 82, 13342–13347 [PubMed: 29131620] f) Wang H, Chen X, Li Y, Wang J, Wu S, Xue W, Yang S, Chi YR, Org. Lett. 2018, 20, 333–336 [PubMed: 29286252] g) Hu Y, Pan D, Cong L, Yao Y, Yu C, Li T, Yao C, ChemistrySelect 2018, 3, 1708–1712.
- [12]. For selected reviews on the o-QDMs, see: a) Segura JL, Martín N, Chem. Rev. 1999, 99, 3199–3246 [PubMed: 11749515] b) Hiroto Y, Joji O, Atsutaka K, Bull. Chem. Soc. Jpn. 2010, 83, 199–219.
- [13]. Chen X, Wang H, Doitomi K, Ooi CY, Zheng P, Liu W, Guo H, Yang S, Song B-A, Hirao H, Chi YR, Nat. Commun. 2017, 8, 15598. [PubMed: 28541276]
- [14]. CCDC 1876027 (**3n**) and CCDC 1888653 (**5n**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [15]. Levens A, An F, Breugst M, Mayr H, Lupton DW, Org. Lett. 2016, 18, 3566–3569. [PubMed: 27434216]
- [16]. a) Wurz NE, Daniliuc CG, Glorius F, Chem. Eur. J. 2012, 18, 16297–16301 [PubMed: 23154931] b) Liu F, Bugaut X, Schedler M, Fröhlich R, Glorius F, Angew. Chem. Int. Ed. 2011, 50, 12626–12630.
- [17]. Ortho-substitution presumably disfavors formation of intermediate **II** through steric effects as has been described before, for recent examples see: a) Borrego LG, Recio R, Alcarranza M, Khiar N, Fernández I, Adv. Synth. Catal. 2018, 360, 1273–1279b) Trost BM, Mata G, Angew. Chem. Int. Ed. 2018, 57, 12333–12337c) Zheng Y, Tan Y, Harms K, Marsch M, Riedel R, Zhang L, Meggers E, J. Am. Chem. Soc. 2017, 139, 4322–4325. [PubMed: 28290685]
- [18]. Alkyl-trifluoromethyl ketones are not compatible under our reaction conditions, presumably due to keto/enol tautomerism as has been described previously (see ref 11d and 17).
- [19]. For selected reviews on the (aza-)o-QMs, see: a) Jaworski AA, Scheidt KA, J. Org. Chem. 2016, 81, 10145–10153 [PubMed: 27513764] b) Yang B, Gao S, Chem. Soc. Rev. 2018, 47, 7926–7953. [PubMed: 29993045]
- [20]. The original work was done using ω B97X/6-311++G(2df,p)/PBE/6-31G(d)/SMD(Toluene). However, the ground state and transition state structures were recomputed at the ω B97XD/6-31G(d)/SMD(Toluene) to account for dispersion interactions present in this system. For computational methodology, see: a) Chai J, Head-Gordon M, J. Chem. Phys. 2008, 10, 6615–6620b) Hehre WJ, Ditchfield R and Pople JA, J. Chem. Phys. 1972, 56, 2257–2261c) Marenich AV, Cramer CJ and Truhlar DG, J. Phys. Chem. 2009, 113, 6378–6396.
- [21]. Bickelhaupt FM, Houk KN, Angew. Chem. Int. Ed. 2017, 56, 10070–10086.

- [22]. Chen S, Zheng Y, Cui T, Meggers E, Houk KN, J. Am. Chem. Soc. 2018, 140, 5146–5152. [PubMed: 29577723]
- [23]. Ess DH, Wheeler SE, Iafe RG, Xu L, Çelebi-Ölçüm N, Houk KN, Angew. Chem. Int. Ed. 2008, 47, 7592–7601.
- [24]. For selected reviews on the (aza)-Petasis-Ferrier rearrangement, see: a) Smith AB, Fox RJ, Razler TM, Acc. Chem. Res. 2008, 41, 675–687 [PubMed: 18489082] b) Minbiole EC, Minbiole KPC, J. Antibiot. 2016, 69, 213 [PubMed: 26732258] For selected examples on the (aza)-Petasis-Ferrier rearrangement, see: c) Smith AB, Minbiole KP, Verhoest PR, Schelhaas M, J. Am. Chem. Soc. 2001, 123, 10942–10953 [PubMed: 11686698] d) Terada M, Toda Y, J. Am. Chem. Soc. 2009, 131, 6354–6355 [PubMed: 19374414] e) Terada M, Komuro T, Toda Y, Korenaga T, J. Am. Chem. Soc. 2014, 136, 7044–7057. [PubMed: 24746095]
- [25]. For reviews on the memory of chirality, see: a) Fuji K, Kawabata T, Chem. Eur. J. 1998, 4, 373–376 b) Kawabata T, Fuji K, In Topics in Stereochemistry, Vol. 23; Denmark SE, Ed.; John Wiley & Sons Inc.: New York, 2003, 175–205 c) Zhao H, Hsu DC, Carlier PR, Synthesis 2005, 1–16 For seminal examples on the memory of chirality, see: d) Seebach D, Wasmuth D, Angew. Chem Int. Ed. Engl. 1981, 20, 971–971 e) Kawabata T, Yahiro K, Fuji K, J. Am. Chem. Soc. 1991, 113, 9694–9696 f) Fuji K, Kawabata T, Chem. Eur. J. 1998, 4, 373–376.
- [26]. For selected reviews on the CF₃-containing drugs, see: a) Wang J, Sánchez-Roselló M, Aceña JL, del Pozo C, Sorochinsky AE, Fustero S, Soloshonok VA, Liu H, Chem. Rev. 2014, 114, 2432–2506 [PubMed: 24299176] b) Zhu W, Wang J, Wang S, Gu Z, Aceña JL, Izawa K, Liu H, Soloshonok VA, J. Fluorine Chem. 2014, 167, 37–54 c) Zhou Y, Wang J, Gu Z, Wang S, Zhu W, Aceña JL, Soloshonok VA, Izawa K, Liu H, Chem. Rev. 2016, 116, 422–518. [PubMed: 26756377]
- [27]. For selected reviews and examples on the synthesis of dihydroquinolones, see: a) Katritzky AR, Rachwal S, Rachwal B, Tetrahedron 1996, 52, 15031–15070 b) Xia Y, Yang Z-Y, Xia P, Bastow KF, Tachibana Y, Kuo S-C, Hamel E, Hackl T, Lee K-H, J. Med. Chem. 1998, 41, 1155–1162 [PubMed: 9544215] c) Tamura SY, Goldman EA, Bergum PW, Semple JE, Bioorg. Med. Chem. Lett. 1999, 9, 2573–2578 [PubMed: 10498211] d) Oshiro Y, Sakurai Y, Sato S, Kurahashi N, Tanaka T, Kikuchi T, Tottori K, Uwahodo Y, Miwa T, Nishi T, J. Med. Chem. 2000, 43, 177–189 [PubMed: 10649973] e) Zhao H, Thurkauf A, Braun J, Brodbeck R, Kieltyka A, Bioorg. Med. Chem. Lett. 2000, 10, 2119–2122 [PubMed: 10999484] f) Nammalwar B, Bunce RA, Molecules 2014, 19, 204–232.

Figure 1.
Dispersion-corrected DFT major and minor [4+2] cycloaddition transition structures.
Distances in Å and energies in kcal/mol.

Figure 2. Potential energy surface plot showing a concerted mechanism for the conversion of **I** and **2a** (See SI).

(a) Annulations via NHC-Bound *o*-QDM Intermediate **(b) Annulation via NHC-Bound *o*-QM Intermediate** **(c) This Work**

Scheme 1.
Generation of NHC-bound *o*-QDMs and *o*-QMs.

Scheme 2.

NHC screening for [4+2] cycloaddition. Conditions: 0.1 mmol **1a**, 0.11 mmol **2a**, 20 μ mol **NHC**, 30 μ mol KHMDS, 50 mg 4 Å MS, 0.1 M in toluene. Absolute configuration of **3a** was determined based on X-ray crystal analysis of **3n**.^[14]

Scheme 3.
Proposed reaction pathways.

Scheme 4.

Transformation of **3**. Conditions: a) Tebbe reagent, toluene/THF, $-40\text{ }^{\circ}\text{C}$ to $25\text{ }^{\circ}\text{C}$; (b) Me_2AlCl , CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$.

Table 1.

Substrate Scope.^[a] ^[a] Reaction scale 0.2 mmol. See the SI for reaction details. Yields reported for compounds isolated. Er determined by chiral-phase SFC analysis.^[b] Performed at 35 °C.