Arylation of Pharmaceutically Relevant Strained Rings Using Electronically Tuned Redox-Active Esters

Daniel C. Salgueiro, Benjamin K. Chi, Pablo Garcia-Reynaga*[b], and Daniel J. Weix*[a]

[a] D. C. Salgueiro, B. K. Chi, Prof. D. J. Weix
Department of Chemistry, University of Wisconsin-Madison
Madison, WI 53706 (USA)
E-mail: dweix@wisc.edu

[b] Dr. P. Garcia-Reynaga
Janssen Research & Development, LLC
3210 Merryfield Row
San Diego, Ca 92121 (USA)

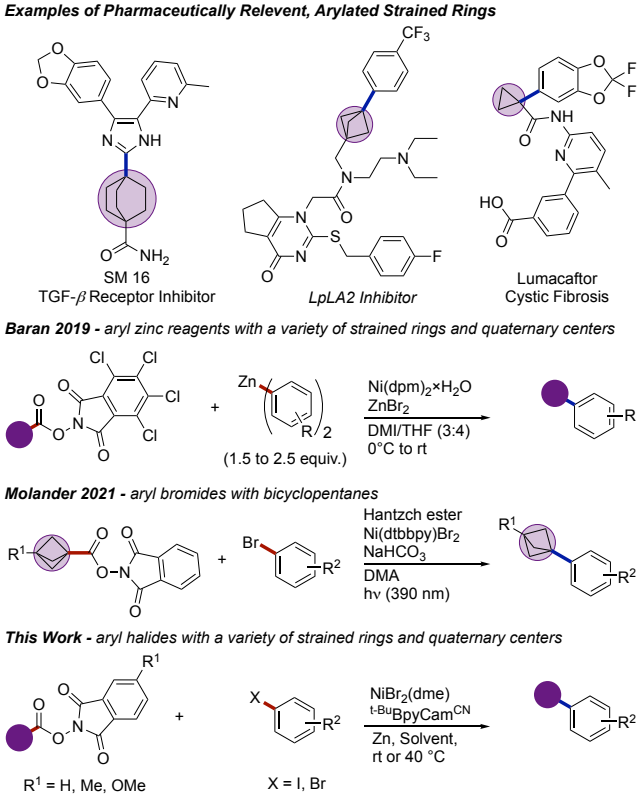
Supporting information for this article is given via a link at the end of the document.

Abstract: *Strained rings are increasingly important for the design of pharmaceutical candidates due to their improved pharmacokinetic and safety profiles, as well as their ability to orient substituents into favorable geometries for the potential improvement of the binding affinity to the biological target. Despite their importance, methodologies to cross-couple strained rings have been underdeveloped. The most abundant source of strained carbocycles and heterocycles is the corresponding carboxylic acid, making methods that employ this substrate pool attractive. Coupling of these carboxylic acids with halides, a second source of abundant building blocks, would allow for rapid access to a diverse set of functionalized carbocyclic and heterocyclic frameworks containing all-carbon quaternary centers. Herein we disclose the development of a nickel-catalyzed cross-electrophile approach that couples a variety of strained ring N-hydroxyphthalimide esters, derived from the carboxylic acid in one step or in situ, with various aryl and heteroaryl halides under reductive conditions. The key to this success was the electronic modification of the NHP ester to make them less reactive, as well as the discovery of a new ligand, $^{t\text{-}Bu}$BpyCam^{CN}, that avoids problematic side reactions. This method enables the incorporation of 3-membered rings, 4-membered rings, and bicyclic fragments onto (hetero)arenes derived from (hetero)aryl iodides and (hetero)aryl bromides, allowing for straightforward and direct access to arylated strained rings.*

Molecules with strained rings, including 3- and 4-membered carbocycles, have gained prominence in medicinal chemistry due to the beneficial effects they impart on the pharmacokinetic and pharmacodynamic properties of drug candidates (Scheme 1).[1] These include improved solubility, metabolic stability, and receptor/ligand binding interactions.[1,2] Most often, incorporation of strained rings into molecules is accomplished by a ring-opening[3] or ring-closing reaction, typically involving a π-system.[4] These annulation reactions are well-studied and can be performed in a stereoselective and regioselective fashion.[4, 5] However, each annulation reaction requires different conditions, and often require multiple steps, making parallel screening of different ring systems difficult.

An ideal strategy to enable the rapid access of these strained ring systems for medicinal chemistry would be a direct cross-coupling approach that would allow access to large pools of coupling partners and be general for a variety of strained rings.[6] Despite advances in strain-release methodologies utilizing "spring-loaded" reagents,[7] and cross-coupling of strained-ring units,[8] current approaches are limited by availability of requisitely functionalized coupling partners and do not yet offer the substrate compatibility and scope needed to rapidly screen a variety of strained-rings.[8] In general, decarboxylative approaches, be they oxidative,[9] redox neutral,[10] or reductive,[11] would be the most attractive due to the widespread availability of strained-ring-containing carboxylic acids.[8,12] Recent studies by Baran[10a] and Molander[13] using NHP esters and Huestis[14] using carboxylates are attractive, but limited by the need for diarylzinc reagents (Baran) or were demonstrated for only bicyclo[1.1.1]pentane (Molander) and amino-oxetane units (Huestis). A general set of conditions that tolerate (hetero)aryl halides and is suited to the incorporation of a variety of strained rings would be ideal.

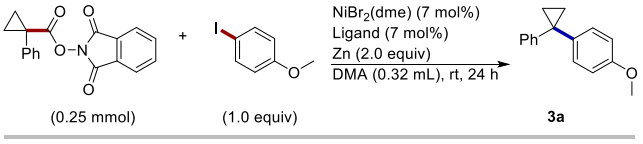
Scheme 1. Arylation of strained rings using tuned redox-active esters.

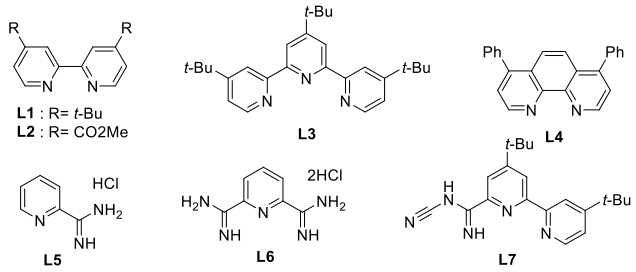


In order to develop a general cross-electrophile coupling of aryl halides with a variety of strained-ring NHP esters, we had to address two major challenges. First, formation of all-carbon

quaternary centers by cross-electrophile coupling remains challenging[15,16] and a limited number of catalysts are reported to be effective. For tertiary radicals of strained rings, which have different catalyst requirements than unstrained tertiary radicals,[17] 2,2'-bipyridine, dtbbpy (**L1**), 4,4'-dicarboxymethyl-2,2'-bipyridine (**L2**), Bphen (**L4**), as well as substituted pyridines and diketonate ligands have been reported to be effective for aryl[10a,13,14,16a-f] and acyl[18] coupling partners. We viewed the identification of additional catalysts as crucial to finding conditions suitable for a wide array of coupling partners. Second, cross-electrophile coupling can be challenging if the relative reactivity of the two substrates is poorly matched.[19] While tuning the reactivity of alkyl halide radical donors by halide choice (iodide, bromide, chloride) or in-situ exchange is broadly useful, few analogous tools for NHP esters exist. Baran found that tetrachloro-NHP esters are significantly more reactive and provided higher yields in cross-coupling with aryl metal reagents.[10] Because NHP esters are already more reactive than alkyl iodides,[11a,c] methods to decrease the reactivity of NHP esters to the level of alkyl bromides would be helpful in cross-electrophile coupling. In theory, *NHP esters could allow a degree of fine-tuning impossible with alkyl halides*.

Table 1. Optimization of the reaction conditions.





Entry[a]	Variation	**3a** Yield (%)[b]
1	**L1**	48
2	**L2**	25
3	**L3**	21
4	**L4**	75
5	**L5**	35
6	**L6**	78
7	**L7** ($^{t\text{-Bu}}$BpyCam^{CN})	92
8	**L7**, Mn as reductant	4
9	no ligand	21
10	no nickel, no ligand	0
11	**L7**, no Zn reductant	0
12	**L7**, THF instead of DMA	72

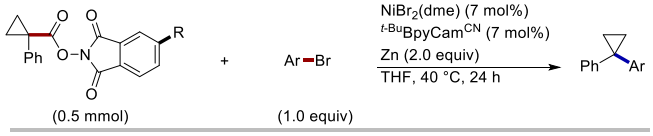
[a] A mixture of NHP ester (0.25 mmol), aryl iodide (0.25 mmol), $NiBr_2$(dme) (7 mol%), ligand (7 mol%), and Zn (0.5 mmol) was stirred at r.t. for 24 h. [b] Corrected GC yield.

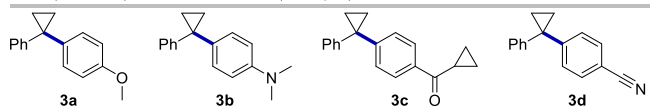
Initial screens began by investigating bidentate amine-type ligands (**L1**-**L4**) as these have been shown to support to nickel-catalyzed cross-electrophile coupling reactions and have been utilized in other reactions with NHP esters (**Table 1**).[11,20] Informed by this precedent, we found that several of these ligands, as well as previously reported amidine ligands (**L5**-**L6**),[21] were effective at promoting the formation of **3a** (entries **1**,**4** and **6**, ligands **L1**, **L4,** and **L6**). However, a new ligand, 4,4′-di-tert-butyl-6-N-cyanocarboxamidine-2,2'-bipyridine ($^{t\text{-Bu}}$BpyCam^{CN}, **L7**) promoted the desired reaction with higher yield due to increased selectivity for the cross-coupled product over alkyl and aryl dimerization reactions. Both a reductant and nickel catalyst are required, and performing the reaction in the absence of a ligand leads to poor selectivity and an overall diminished yield (entries **9-11**). Reactions with only zinc metal, in the absence of nickel catalyst, led to only minor conversion of NHP ester (entry **10**). This suggests that zinc alone is not efficient at promoting the reduction of the NHP ester under these conditions.[22] Although the reaction in THF resulted in a lower yield (entry **13**), this solvent has been shown to slow the consumption of NHP esters, which we hypothesized would allow for better rate matching with coupling partners that are slower to undergo oxidative addition.

We observed that aryl bromides gave poor yields of product. These reactions consumed the NHP ester, but not the aryl bromide, suggesting that the reactivity difference between the NHP ester and the aryl bromide was too great for cross-electrophile coupling to be selective. We hypothesized that electronic modification of the phthalimide fused arene by the incorporation of electron donating functional groups could be used to modulate the reduction potential (and therefore reactivity) of the resulting NHP esters (**Table 2**). While the more reactive

Table 2. Electronic tuning of NHP esters.[a]

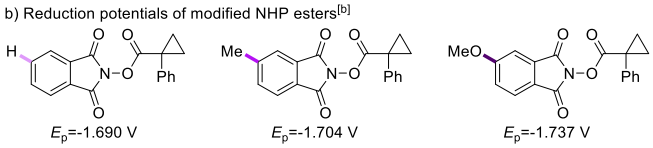
a) Coupling of modified NHP esters with aryl bromides





3a	3b	3c	3d
R = H, <5%	R = H, <5%	R = H, 30%	R = H, 47%
R = Me, 18%	R = Me, 22%	R = Me, 50%	R = Me, 62%
R = OMe, 38%	R = OMe, 27%	R = OMe, 60%	R = OMe, 53%

b) Reduction potentials of modified NHP esters[b]

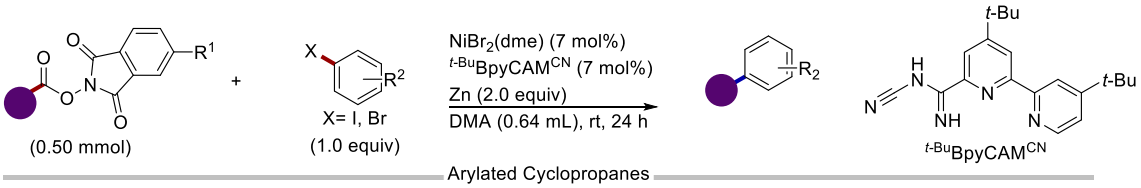


[a] A mixture of NHP ester (0.5 mmol), aryl bromide (0.5 mmol), NiBr2(dme) (7 mol%), $^{t\text{-Bu}}$BpyCam^{CN} (7 mol%), and Zn (1.0 mmol) was stirred at 40 °C in THF for 24 h. Yields are isolated yields after purification.[b] Peak potentials for the cathodic wave (reduction) listed are vs Fc^+/Fc in 0.1 M $TBAPF_6$ in DMF.

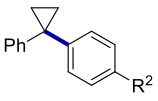
tetrachloro *N*-hydroxyphthalimide has been used to increase reactivity in couplings with organometallic reagents,[10a] this strategy of using redox tuned NHP esters has not been used to *slow down* decarboxylative radical formation in cross-coupling reactions. Consistent with our hypothesis, the introduction of electron donating substituents onto the 4-position of *N*-hydroxyphthalimide led to notable changes to the reduction potentials of the corresponding esters (**Table 2b**). This change in reduction potential, in conjunction with the use of THF as solvent,

led to improvements in yields for the coupling of both electron-rich and electron-deficient aryl bromides, particularly in cases where the the standard NHP ester was entirely consumed prior to full consumption of the aryl bromide.

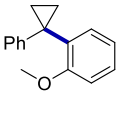
Table 3. Substrate scope for the decarboxylative coupling of strained-ring NHP esters with (hetero)aryl halides.[a]



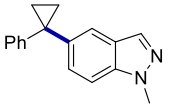
Arylated Cyclopropanes



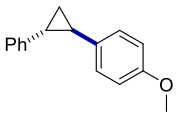
3a R^1= H, R^2=OMe, X=I, 75%, 56%[b], R^1=OMe, X=Br: 38%[c],[d]
3b R^1=OMe, R^2=NMe_2, X=Br, 27%[c],[d]
3c R^1=OMe, R^2=C(O)-*c*-C_3H_5, X=Br, 60%[c],[d]
3d R^1=H, R^2=CN, X=I, 64%
R^1=Me, R^2=CN, X=Br, 62%[c],[d]
3e R^1=H, R^2=*t*-Bu, X=I 72%
3f R^1=H, R^2=BPin, X=I 62%



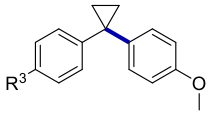
3g R^1=H, X=I
41%[e]



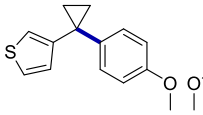
3h R^1=H, X=I
43%



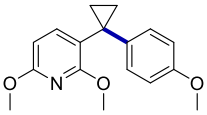
3i R^1=H, X=I
36%



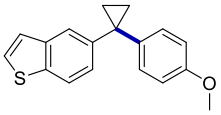
3j R^1=H ,R^3=OMe, X=I, 71%[f]
3k R^1=H ,R^3=Cl, X=I, 40%[f]



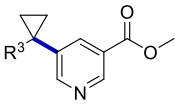
3l R^1=H, X=I
57%[f]



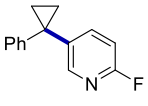
3m R^1=H, X=I
94%[f]



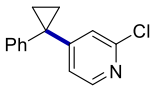
3n R^1=H, X=I
77%[f]



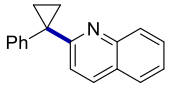
3o R^1=H, X=Br, R^3=Ph, 55%[c],[d]
3p R^1=H, X=Br, R^3=Me, 42%[c],[d],[f],[g]



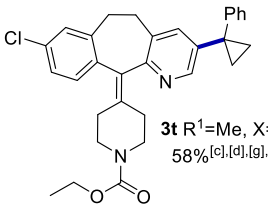
3q R^1=H,X=Br
25%[c],[d]



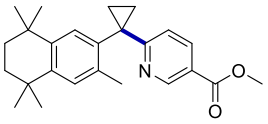
3r R^1=H, X=Br
56%[c],[d]



3s R^1=H, X=Br
29%[c]

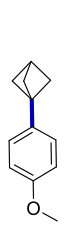


3t R^1=Me, X=Br
58%[c],[d],[g],[h]

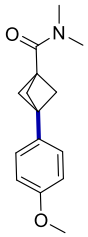


3u R^1=H, X=Br
21%[f]

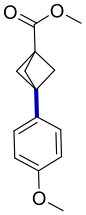
Arylated Bicyclo[1.1.1]pentanes



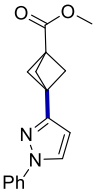
3v R^1=OMe, X=I
42%[g],[i],[j]



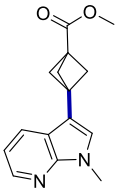
3w R^1=H, X=I
52%[g],[i],[j]



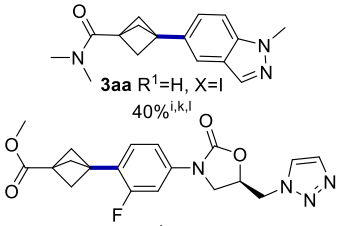
3x R^1=H, X=I
40%[c]



3y R^1=H, X=I
51%[g],[i],[j]



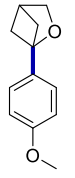
3z R^1=H, X=I
31%[g],[i],[j]



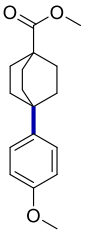
3aa R^1=H, X=I
40%[i,k,l]

3ab R^1=H, X=I
15%[g],[i],[j]

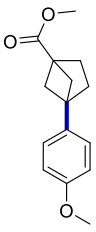
Other Strained Rings



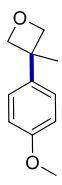
3ac R^1=H, X=I
32%[f],[i]



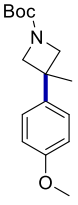
3ad R^1=H, X=I
39%



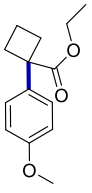
3ae R^1=H, X=I
22%[g],[i],[j]



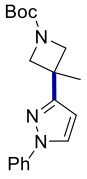
3af R^1=H, X=I
49%[c]



3ag R^1=H, X=I
60%[c],[g],[j]



3ah R^1=H, X=I
39%[c]



3ai R^1=H, X=I
71%[g],[i],[j]

[a] Reactions were performed at a 0.5 mmol scale in 0.64 mL of DMA for 24 h. Yields are isolated yields after purification. [b] NHP ester was generated in situ. [c] Reaction was carried out in THF. [d] Reaction was carried out at 40 °C. [e] Bathophenanthroline (**L4**) was used as the ligand. [f] Reaction was carried out at 0.25 mmol scale. [g] Reaction was carried out with 20 mol% nickel and ligand. [h] Reaction was carried out at 0.10 mmol scale. [i] Reaction was carried out in a 9:1 mixture of THF:DMA. [j] Reaction was carried out at 0.300 mmol scale.

Applying the optimized conditions to a variety of different carboxylic acid and aryl halide pairs demonstrated the utility of this method for the synthesis of diaryl cyclopropanes, a useful replacement for 1,1-diarylalkenes and diarylmethanes[8, 23] Optimized conditions employ a 1:1 stoichiometry of NHP ester and (hetero)aryl halide and a typical catalyst loading of 7 mol%, although increasing the catalyst loading to 20 mol% led to improved yields in some cases (**Table 3**). A variety of arene-based functionalities that enable subsequent elaboration, such as nitriles (**3d**), chlorides (**3k**, **3r**, **3t**), esters (**3o**, **3p**, **3u**), and pinacol boronate esters (**3f**) were tolerated. Notably, an aryl iodide bearing a substituent in the ortho position (**3g**) did not work well with the tridentate **L7**, but did work in moderate yield with bidentate **L4**. Less reactive aryl coupling partners such as aryl bromides (**3a**, **3b**, **3c**, **3d**) and heteroaryl bromides (**3o**, **3p**, **3q**, **3r**, **3s**, **3t**, **3u**) can also engage in the cross-coupling reaction by changing the reaction solvent to THF and elevating the temperature. Coupling can be achieved at the 2, 3, and 4 position of pyridine and pyridine-like heterocycles (**3o**, **3p**, **3q**, **3r**, **3s**, **3t**, **3u**). Aryl bromides derived from pyrazole, pyrrolopyridine, and indazole heterocycles can also be coupled in good yields (**3h**, **3y**, **3z**, **3aa**, **3ai**). For rapid syntheses of analogues, carboxylic acids can be converted to the NHP ester and coupled in one pot, albeit with decreased yield (From 75% with the isolated NHP ester to 56% with in situ generated NHP ester). Additionally, the reaction can be scaled up to 3 mmol scale in batch mode to afford **3a** in 63% yield (see **SI Section 3.3.3**.)

One potential advantage of our approach is that 1,1-diarylcyclopropanes can be synthesized in a modular fashion from two different aryl halides and cyclopropane carboxylic acid using α-arylation and decarboxylative cross-electrophile coupling. Using α-arylation conditions recently reported by Hartwig,[24] we were able to rapidly synthesize several alternative NHP esters. Changing the arene of benzylic cyclopropyl NHP esters was well tolerated (**3j**, **3k**, **3l**, **3m**, **3n**). We demonstrate the utility of this approach for the flexible construction of drug-like molecules through the preparation of the methyl ester of LG100268 **3u**, a more potent and specific cyclopropyl analogue of the only FDA-approved RXR agonist Bexarotene.[25] The advantage of our approach is that it allows for facile modification of the right-side C-ring, providing a route for the synthesis of a library of analogues. Non-benzylic secondary and tertiary strained ring NHP esters (**3i**, **3p**) are tolerated under these conditions but are lower yielding, presumably due to the lower stability of the corresponding radicals. Notably, NHP esters bearing additional ester functionality can be successfully coupled, providing an easy entry for sequential arylation of bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, and cyclobutene ring systems (**3x**, **3ad**, **3ae, 3ah)**. Other pharmaceutically relevant ring systems such as the NHP esters derived from bicyclo[1.1.1]pentane (**3v-3ab**), 2-oxabicyclo[2.1.1]hexane (**3ac**) bicyclo[2.2.2]octane (**3ad**), bicyclo[2.1.1]hexane (**3ae**), oxetane (**3af**), azetidine (**3ag**, **3ai**), and, cyclobutane(**3ah**) ring systems were also coupled in good yield.

We also found that this reaction could be scaled up in flow[26] using the zinc packed-bed strategy of Ley.[266c] Without any additional optimization, a solution of bicyclo[1.1.1]pentane NHP ester and anisyl iodide along with catalyst (20 mol%) was passed through a column of activated zinc at 30 °C, resulting in a 51% yield of **3x** (**Figure 1**).

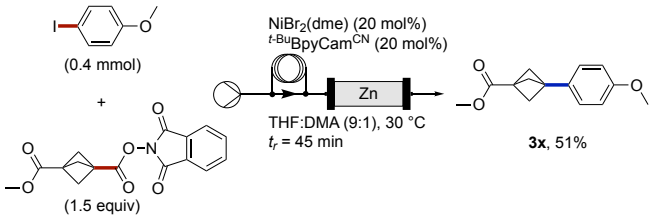


Figure 1. Synthesis of **3x** under continuous flow using conditions adapted from Ley and coworkers.[26c]

Although we have yet to study the mechanism of this reaction in detail, similarities to other cross-electrophile couplings[11a] with NHP esters and aryl halides implicates an analogous mechanism: (a) initial oxidative addition of the aryl halide to nickel(0) followed by (b) oxidative radical capture by the resulting arylnickel(II) intermediate. (c) Reductive elimination from the resulting bisorgano-nickel(III) species gives the desired product with concomitant formation of a nickel(I) intermediate. The formation of radicals from NHP esters can be mediated by nickel or arise from direct reduction with zinc, assisted by Lewis acid coordination to the NHP ester, although our control experiments suggest that direct reduction by zinc is a minor pathway (**Table 1**, entry 9).

In conclusion, we have expanded the scope of decarboxylative C(sp^3)–C(sp^2) cross-electrophile coupling to include several different classes of pharmaceutically-relevant strained rings and achieved reliable coupling of NHP esters with (hetero)aryl bromides and iodides. This is enabled by a new, selective ligand ($^{t\text{-Bu}}$BpyCam^{CN}), and the tuning of NHP ester reduction potentials by altering the substituents on the phthalimide backbone. We envision that further tuning of NHP ester reduction potentials will allow access to couplings of more challenging substrate pools, expanding the utility of redox active esters as a tool for C–C bond formations. Further mechanistic work to better understand the effect of electronic modification of NHP esters and optimization of this chemistry in flow format are underway.

Acknowledgements

Research reported in this publication was supported by the NIH under award number R01GM097243 (to DJW), the NSF under DGE-1747503 (to DCS), Janssen (PGR, DCS), and the Graduate School and the Office of the Vice Chancellor for Research and Graduate Education at the University of Wisconsin-Madison with funding from the Wisconsin Alumni Research Foundation. Instrumentation in the PBCIC was supported by NSF grant CHE-1048642 (Bruker AVANCE 400) and Paul J. and Margaret M. Bender (Bruker AVANCE 500). We thank Dr. Jiang Wang (UW-Madison), Dr. Kai Kang (UW-Madison), Dr. Michael K. Ameriks (Janssen), Dr. Zhi-Cai Shi (Janssen), Michelle Akana (UW-Madison), and Jonas Widness (UW-Madison) for helpful insights.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: cross-electrophile coupling • nickel catalysis • redox-active esters • strained rings • quaternary centers

[1] a) M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer, B. C. Whitehurst, *RSC Med. Chem.* **2021**, *12*, 448–471. b) A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926–4996. c) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756. d) F. Lovering, *MedChemComm* **2013**, *4*, 515. e) K. Kuk, J. L. Taylor-Cousar, *Ther Adv Respir Dis* **2015**, *9*, 313–326. f) E. Suzuki, S. Kim, H.-K. Cheung, M. J. Corbley, X. Zhang, L. Sun, F. Shan, J. Singh, W.-C. Lee, S. M. Albelda, L. E. Ling, *Cancer Res* **2007**, *67*, 2351–2359. g) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem.* **2012**, *55*, 3414–3424.

[2] a) A. de Meijere, *Angew. Chem. Int. Ed. in English* **1979**, *18*, 809–826. b) T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756. c) C. M. Marson, *Chemical Society Reviews* **2011**, *40*, 5514–5533. d) F. Toselli, M. Fredenwall, P. Svensson, X.-Q. Li, A. Johansson, L. Weidolf, M. A. Hayes, *J. Med. Chem.* **2019**, *62*, 7383–7399.

[3] a) M. Messner, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem* **2000**, *2000*, 1137–1155. b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209–3226.

[4] a) M. D'Auria, *Photochem. Photobiol. Sci.* **2019**, *18*, 2297–2362. b) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783–816. c) M. A. Ischay, M. S. Ament, T. P. Yoon, *Chem. Sci.* **2012**, *3*, 2807. d) G. De Faveri, G. Ilyashenko, M. Watkinson, *Chem. Soc. Rev.* **2011**, *40*, 1722–1760. e) A. Padwa, S. S. Murphree, **2006**, 28. f) M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*, 14046–14128. g) A. Luque, J. Paternoga, T. Opatz, , *Chem. Eur. J.* **2021**, *27*, 4500–4516. h) V. V. Levterov, Y. Panasyuk, V. O. Pivnytska, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2020**, *59*, 7161–7167.

[5] a) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485–1538. b) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651–11679.

[6] A. W. Dombrowski, N. J. Gesmundo, A. L. Aguirre, K. A. Sarris,J. M. Young, A. R. Bogdan, M. C. Martin, S. Gedeon, Y. Wang, *ACS Med. Chem. Lett.* **2020**, *11*, 597–604.

[7] a) J. Turkowska, J. Durka, D. Gryko, *Chem. Commun.* **2020**, *56*, 5718–5734. b) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241–246. c) E. W. Delia, I. J. Lochert, *Org. Prep. Proced. Int.* **1996**, *28*, 411–441. d) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774–12777. e) S. Hoz, D. Aurbach, *Tetrahedron* **1979**, *35*, 881–883. f) R. Gianatassio, D. Kadish, *Org. Lett.* **2019**, *21*, 2060–2063. f) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568–9574. g) H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, *J. Am. Chem. Soc.* **2021**, *143*, 9729–9736. h) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan, *Nature* **2020**, *580*, 220–226.

[8] a) M. R. Harris, H. M. Wisniewska, W. Jiao, X. Wang, J. N. Bradow, *Organic Letters* **2018**, *20*, 2867–2871. b) G. A. Molander, P. E. Gormisky, *J. Org. Chem.* **2008**, *73*, 7481–7485. c) M. D. VanHeyst, J. Qi, A. J. Roecker, J. M. E. Hughes, L. Cheng, Z. Zhao, J. Yin, *Org. Lett.* **2020**, *22*, 1648-1654. d) J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson, *Angew. Chem. Int. Ed.* **2020**, *59*, 11866–11870. e) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C MacMillan, *Nature* **2020**, *580*, 220–226. f) M. Ociepa, A. J. Wierzba, J. Turkowska, D. Gryko, *J. Am. Chem. Soc.* **2020**, *142*, 5355–5361. g) L. R. Mills, J. J. Monteith, G. dos Passos Gomes, A. Aspuru-Guzik, S. A. L. Rousseaux, *J. Am. Chem. Soc.* **2020**, *142*, 13246–13254. h) Z. Dong, D. W. C. MacMillan, *Nature* **2021**, *598*, 451–456.

[9] a) R. A. Daley, A. S. Morrenzin, S. R. Neufeldt, J. J. Topczewski, *J. Am. Chem. Soc.* **2020**, *142*, 13210–13218. b) Z. Luo, X. Han, Y. Fang, P. Liu, C. Feng, Z. Li, X. Xu, *Org. Chem. Front.* **2018**, *5*, 3299–3305.

[10] a) T.-G. Chen, H. Zhang, P. K. Mykhailiuk, R. R. Merchant, C. A. Smith, T. Qin, P. S. Baran, *Angew. Chem. Int. Ed.* **2019**, *58*, 2454–2458. b) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177.

[11] a) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019. b) J. Wang, M. E. Hoerrner, M. P. Watson, D. J. Weix, *Angew. Chem. Int. Ed.* **2020**, *59*, 13484–13489. c) H. Li, C. P. Breen, H. Seo, T. F. Jamison, Y.-Q. Fang, M. M. Bio, *Org. Lett.* **2018**, *20*, 1338–1341. d) L. M. Kammer, S. O. Badir, R.-M. Hu, G. A. Molander, *Chem. Sci.* **2021**, *12*, 5450–5457. e) D. T. Flood, S. Asai, X. Zhang, J. Wang, L. Yoon, Z. C. Adams, B. C. Dillingham, B. B. Sanchez, J. C. Vantourout, M. E. Flanagan, D. W. Piotrowski, P. Richardson, S. A. Green, R. A. Shenvi, J. S. Chen, P. S. Baran, P. E. Dawson, *J. Am. Chem. Soc.* **2019**, *141*, 9998–10006.

[12] a) R. C. Mykura, P. Songara, E. Luc, J. Rogers, E. Stammers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2021**, *60*, 11436–11441. b) R. Davenport, M. Silvi, A. Noble, Z. Hosni, N. Fey, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, 59, 6525 –6528 c) A. Fawcett, A. Murtaza, C. H. U. Gregson, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 4573–4578.

[13] V. C. Polites, S. O. Badir, S. Keess, A. Jolit, G. A. Molander, *Org. Lett.* **2021**, *23*, 4828–4833.

[14] K. Kolahdouzan, R. Khalaf, J. M. Grandner, Y. Chen, J. A. Terrett, M. P. Huestis, *ACS Catal.* **2020**, *10*, 405–411.

[15] W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin, H. Gong, *Chem. Soc. Rev.* **2021**, *50*, 4162–4184.

[16] a) X. Wang, S. Wang, W. Xue, H. Gong, *J. Am. Chem. Soc.* **2015**, *137*, 11562–11565. b) X. Lu, Y. Wang, B. Zhang, J.-J. Pi, X.-X. Wang, T.-J. Gong, B. Xiao, Y. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 12632–12637. c) Y. Ye, H. Chen, J. L. Sessler, H. Gong, *J. Am. Chem. Soc.* **2019**, *141*, 820–824. d) Y. Peng, L. Luo, C.-S. Yan, J.-J. Zhang, Y.-W. Wang, *J. Org. Chem.* **2013**, *78*, 10960–10967. e) X. Wang, G. Ma, Y. Peng, C. E. Pitsch, B. J. Moll, T. D. Ly, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2018**, *140*, 14490–14497. f) Z. Wang, Z. P. Yang, G. C. Fu, *Nat. Chem.* **2021**, 13, 236–242. g) M. Börjesson, T. Moragas, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 7504–7507.

[17] a) H. M. Walborsky, *Tetrahedron* **1981**, *37*, 1625–1651. b) A. Veillard, G. Re, *Theoret. Chim. Acta* **1964**, *2*, 55–62. c) M. Yuan, Z. Song, S. O. Badir, G. A. Molander, O. Gutierrez, *J. Am. Chem. Soc.* **2020**, 142, 7225–7234.

[18] a) J. Wang, B. P. Cary, P. D. Beyer, S. H. Gellman, D. J. Weix, *Angew. Chem. Int. Ed.* **2019**, *58*, 12081–12085. b) S. Ni, N. M. Padial, C. Kingston, J. C. Vantourout, D. C. Schmitt, J. T. Edwards, M. M. Kruszyk, R. R. Merchant, P. K. Mykhailiuk, B. B. Sanchez, S. Yang, M. A. Perry, G. M. Gallego, J. J. Mousseau, M. R. Collins, R. J. Cherney, P. S. Lebed, J. S. Chen, T. Qin, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6726–6739. c) X. Xi, Y. Luo, W. Li, M. Xu, H. Zhao, Y. Chen, S. Zheng, X. Qi, W. Yuan, *Angew. Chem. Int. Ed.* **2021**, *60*, 2 – 10.

[19] a) S. Kim, M. J. Goldfogel, M. M. Gilbert, D. J. Weix, *J. Am. Chem. Soc.* **2020**, *142*, 9902–9907. b) D. A. Everson, D. J. Weix, *J. Org. Chem.* **2014**, *79*, 4793–4798. c) D. A. Everson, B. A. Jones, D. J. Weix, *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.

[20] L. Huang, A. M. Olivares, D. J. Weix, *Angew. Chem. Int. Ed.* **2017**, *56*, 11901–11905.

[21] a) E. C. Hansen, C. Li, S. Yang, D. Pedro, D. J. Weix, *J. Org. Chem.* **2017**, *82*, 7085–7092. b) E. C. Hansen, D. J. Pedro, A. C. Wotal, N. J. Gower, J. D. Nelson, S. Caron, D. J. Weix, *Nature Chem* **2016**, *8*, 1126–1130.

[22] W.-T. Jiang, S. Yang, M.-Y. Xu, X.-Y. Xie, B. Xiao, *Chem. Sci.* **2020**, *11*, 488–493.

[23] a) J. X. Qiao, D. L. Cheney, R. S. Alexander, A. M. Smallwood, S. R. King, K. He, A. R. Rendina, J. M. Luettgen, R. M. Knabb, R. R. Wexler, P. Y. S. Lam, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4118–4123. b) M. F. Boehm, L. Zhang, L. Zhi, M. R. McClurg, E. Berger, M. Wagoner, D. E. Mais, C. M. Suto, P. J. A. Davies, R. A. Heyman, A. M. Nadzan, *J. Med. Chem.* **1995**, *38*, 3146–3155. c) C. E. Wagner, P. W. Jurutka, P. A. Marshall, T. L. Groy, A. van der Vaart, J. W. Ziller, J. K. Furmick, M. E. Graeber, E. Matro, B. V. Miguel, I. T. Tran, J. Kwon, J. N. Tedeschi, S. Moosavi, A. Danishyar, J. S. Philp, R. O. Khamees, J. N. Jackson, D. K. Grupe, S. L. Badshah, J. W. Hart, *J. Med. Chem.* **2009**, *52*, 5950–5966.

[24] Z.-T. He, J. F. Hartwig, *Nat Commun* **2019**, *10*, 4083.

[25] a) A. S. Leal, K. Zydeck, S. Carapellucci, L. A. Reich, D. Zhang, J. A. Moerland, M. B. Sporn, K. T. Liby, *npj Breast Cancer* **2019**, *5*, 39. b) J. D. Love, J. T. Gooch, S. Benko, C. Li, L. Nagy, V. K. K. Chatterjee, R. M. Evans, J. W. R. Schwabe, *J. Biol. Chem.* **2002**, *277*, 11385–11391. c) M. F. Boehm, L. Zhang, L. Zhi, M. R. McClurg, E. Berger, M. Wagoner, D. E. Mais, C. M. Suto, P. J. A. Davies, R. A. Heyman, A. M. Nadzan, *J. Med. Chem.* **1995**, *38*, 3146–3155.

[26] a) N. Alonso, L. Z. Miller, J. de M. Muñoz, J. Alcázar, D. T. McQuade, *Adv. Synth. Catal.* **2014**, *356*, 3737–3741. b) M. Berton, L. Huck, J. Alcázar, *Nat Protoc* **2018**, *13*, 324–334. c) E. Watanabe, Y. Chen, O. May, S. V. Ley, *Chem. Eur. J.* **2020**, *26*, 186–191.