Tandem Pd-catalyzed C-C coupling/recyclization of 2-(2-bromoaryl)cyclopropane-1,1-dicarboxylates with primary nitro alkanes

Andrey A. Mikhaylov, Alexander D. Dilman, Roman A. Novikov, Yulia A. Khoroshutina, Marina I. Struchkova, Dmitry E. Arkhipov, Yulia V. Nelyubina, Andrey A. Tabolin, Sema L. Ioffe

PII: S0040-4039(15)30288-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.10.091
Reference: TETL 46920

To appear in: *Tetrahedron Letters*

Received Date: 7 September 2015
Revised Date: 19 October 2015
Accepted Date: 27 October 2015

Please cite this article as: Mikhaylov, A.A., Dilman, A.D., Novikov, R.A., Khoroshutina, Y.A., Struchkova, M.I., Arkhipov, D.E., Nelyubina, Y.V., Tabolin, A.A., Ioffe, S.L., Tandem Pd-catalyzed C-C coupling/recyclization of 2-(2-bromoaryl)cyclopropane-1,1-dicarboxylates with primary nitro alkanes, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.10.091

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Tandem Pd-catalyzed C-C coupling/recyclization of 2-(2-bromoaryl)cyclopropane-1,1-dicarboxylates with primary nitro alkanes

Andrey A. Mikhaylov,[a,*] Alexander D. Dilman,[a] Roman A. Novikov,[a] Yulia A. Khoroshutina,[a] Marina I. Struchkova,[a] Dmitry E. Arkhipov,[b,c] Yulia V. Nelyubina,[b] Andrey A. Tabolin,[a] Sema L. Ioffe [a,*]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prosp. 47, 119991 Moscow, Russian Federation;*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova str. 28, 119991 Moscow, Russian Federation;*
[c] *N. I. Pirogov Russian National Research Medical University, Ostrovityanova str. 1, 117997 Moscow, Russian Federation*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

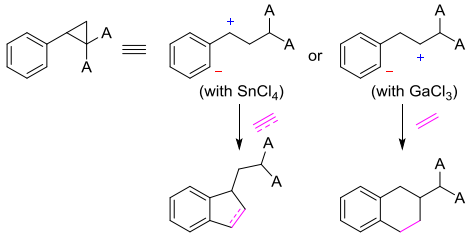
Keywords:
Palladium-catalysis
Cross-coupling reactions
Tandem reactions
Nitroalkanes
Donor-acceptor cyclopropanes

ABSTRACT

The first successful synthesis of 1*H*-2,3-benzoxazine 3-oxides has been described. The efficiency of the approach is provided by the C-C-coupling of 2-(2-bromoaryl)cyclopropane-1,1-dicarboxylates with primary nitroalkanes catalyzed by $Pd(dba)_2$/JohnPhos system followed by *in situ* recyclization of the intermediates. Several representative transformations allowing selective modification of the nitronate as well as malonate functionalities in the resulting compounds are demonstrated.

1. Introduction

One of the most promising recent advances in the chemistry of ring-strain molecules is associated with donor-acceptor (DA) cyclopropanes.[1-5] The weak and polarized endocyclic bond in these substrates provides various opportunities for nucleophilic ring opening,[1,2] isomerizations,[1f,g] Lewis acid mediated cycloadditions,[1e,3] annulations[4] and cyclodimerizations.[1h,5] When the aryl substituent plays the role of donor fragment, additional possibilities for ring formation *via* Friedel-Crafts annulation onto the *ortho*-position of the arene moiety arise depending on the choice of Lewis acid used for activation of the cyclopropane fragment (Scheme 1). Thus, $SnCl_4$ catalyzes the generation of formal 1,3-dipoles and their condensation with alkenes[4a,5a] or alkynes,[4b] resulting in an indane fragment. At the same time $GaCl_3$ generates formal 1,4-dipoles, which can be transformed into various tetralins.[5b]



Scheme 1. Annulations with aryl-substituted DA cyclopropanes.

In this manuscript we suggest another approach for benzannulation based on (2-bromoaryl)cyclopropanes **1** (Figure 1). The latter could be regarded as 1,3-dicationic synthons with two entirely different electrophilic centers. In this context, an appropriate binucleophilic partner for substrates **1** is required. As the most promising reagent of this kind, primary nitro alkanes **2** were chosen due to their ability to behave as *C*- and *O*-nucleophiles.[6]

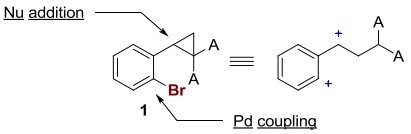
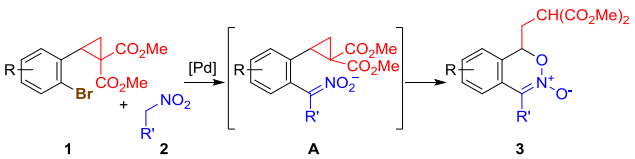


Figure 1. (2-Bromoaryl)cyclopropanes as 1,3-dicationic synthons.

Given that the recently developed palladium catalyzed cross-coupling reactions of nitro compounds with aryl halogenides exclusively provides *C*-arylation products,[7] further cyclopropane ring opening by the nitronate oxygen in intermediate **A** could lead to previously unknown 1*H*-2,3-benzoxazines 3-oxides **3** (Scheme 2).



Scheme 2. Our strategy for the synthesis of nitronates **3.**

Compounds **3** belong to a scarcely known class of 1,2-oxazine-2-oxides. While common six-membered cyclic nitronates (5,6-dihydro-4*H*-1,2-oxazine-2-oxides) are readily available *via* the hetero Diels-Alder reaction of nitroalkenes with olefins (Figure 2, (1)),[8,9] the synthesis of unsaturated six-

membered cyclic nitronates is much more complicated. In fact, only two examples of these compounds are present in the literature (Figure 2, compounds **4** and **5**).[10,11] 6*H*-1,2-Oxazine-2-oxides exist in equilibrium with nitrodienes with the latter generally being thermodynamically preferred.[10] Fusion with an aromatic ring makes these compounds much more stable, however only coumarin derivative **5** has been described.[11]

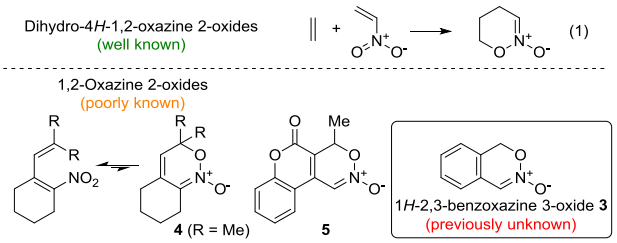


Figure 2. Benzoxazine *N*-oxides and related compounds.

Herein we propose a general approach for the synthesis of benzannulated nitronates **3** which could significantly broaden the scope of available oxazine-*N*-oxides.[12]

2. Results and discussion

Starting (2-bromoaryl)cyclopropanes **1** were easily available either by Corey-Chaykovsky cyclopropanation of the corresponding arylidenemalonates or by the reaction of 2-bromostyrenes with diazomalonate.[13]

Table 1. Optimization of the reaction conditions[a]

entry	"Pd" source	ligand **L**	base	yield **3aa** (%)[b]
1	$Pd(OAc)_2$ (2.5 mol%)	XantPhos[c] (5 mol%)	*t*BuOK (1.3 equiv)	– (<5)
2	$Pd(OAc)_2$ (2.5 mol%)	JohnPhos[d] (7.5 mol%)	*t*BuOK (1.3 equiv)	5 (10)
3	$Pd(dba)_2$ (2.5 mol%)	JohnPhos (5 mol%)	*t*BuOK (1.3 equiv)	10 (15)
4	$Pd(dba)_2$ (5 mol%)	JohnPhos (10 mol%)	*t*BuOK (1.3 equiv)	25 (27)
5	$Pd(dba)_2$ (5 mol%)	JohnPhos (10 mol%)	*t*BuOK (2.0 equiv)	30 (31)
6	$Pd(dba)_2$ (5 mol%)	JohnPhos (10 mol%)	Cs_2CO_3 (2.0 equiv)	45 (52)
7	$Pd(dba)_2$ (10 mol%)	JohnPhos (20 mol%)	Cs_2CO_3 (2.0 equiv)	76 (100)
8	$Pd_2(dba)_3$[e] (5 mol%)	JohnPhos (20 mol%)	Cs_2CO_3 (2.0 equiv)	74 (100)

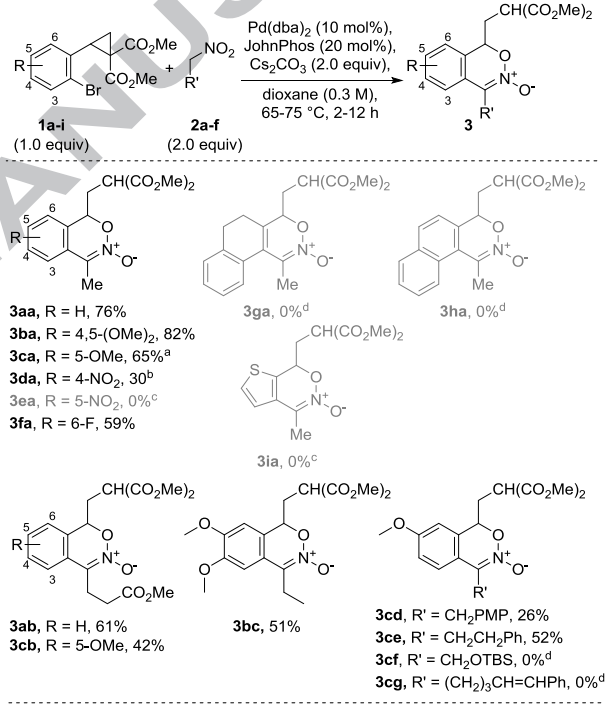
[a] Dimethyl 2-(2-bromophenyl)-1,1-cyclopropanedicarboxylate **1a** (1.0 equiv), nitroethane **2a** (2.0 equiv), **L**, base, dioxane (0.3 M), 65-75 °C, 2-24 h. For details see ESI;
[b] determined by NMR with an internal standard, in parentheses – conversion of the initial cyclopropane **1a**;
[c] 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene;
[d] (2-biphenyl)di-*tert*-butylphosphine;
[e] $Pd_2(dba)_3$•$CHCl_3$.

In preliminary experiments we found that 2-bromophenyl-substituted substrate **1a** and nitroethane **2a** could be coupled in the presence of a palladium catalyst, affording benzoxazine *N*-oxide **3aa** (Table 1). Optimization of the reaction conditions showed that JohnPhos was an optimal ligand and not less than 5 mol% of [Pd] was necessary for reasonable conversions of the initial cyclopropane **1a** (Table 1, *cf.* entries 1-4). $Pd(dba)_2$ was found to be the precatalyst of choice, which was in accordance with literature data.[7] Surprisingly, the reaction was very sensitive to the selection of base, with the best results being obtained with 2.0 equiv of Cs_2CO_3. The addition of 10 mol% of [Pd] was required for full conversion of the initial bromocyclopropane **1a** (entries 7-8) and gave nitronate **3aa** in 76% and 74% yield with $Pd(dba)_2$ or $Pd_2(dba)_3$•$CHCl_3$, respectively. The necessity for high catalyst loadings could be associated with the steric hindrance of the α-cyclopropyl moiety, which makes the oxidative addition step challenging.

Note that the reaction proceeded quickly, and generally was complete within 2-4 hours at 65-75 °C. After this period no further conversion of the initial cyclopropane **1a** occurred. In the reaction mixture even traces of intermediate **A** (see Scheme 2) or its protonated form arising from primary palladium coupling could not be detected. Evidently, the recyclization of the cyclopropane moiety proceeds faster than cross-coupling.

Reactions conducted with aged palladium precatalyst lacked reproducibility, so only fresh $Pd(dba)_2$ should be utilized in this process. However, in several cases, the catalytic activity for old samples of $Pd(dba)_2$ could be reinstated after its conversion into $Pd_2(dba)_3$•$CHCl_3$.

Table 2. Series of 1*H*-2,3-benzoxazine 3-oxides **3**.



[a] 5% $Pd_2(dba)_3$•$CHCl_3$ was used instead of $Pd(dba)_2$;
[b] yield according to ^1H NMR using $CHCl=CCl_2$ as the internal standard;
[c] complex mixture of products;
[d] 15% $Pd(dba)_2$, 30% JohnPhos were used, conversion <5% after 8-12 hours.

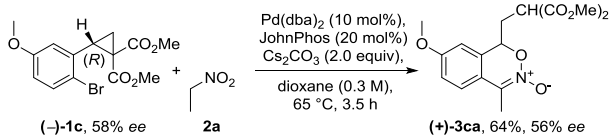
The reaction scope was briefly examined under the optimized conditions (Table 2). Cyclopropanes **1b-f,** with various substituents on the phenyl ring, and nitroethane **2a** were initially studied in this process. Substrates with electron-donating methoxy-groups **1b** (4,5-di-OMe) and **1c** (5-OMe) reacted faster than unsubstituted cyclopropane **1a** and gave the corresponding nitronates **3ba** and **3bc** in good yields. For nitro-substituted cyclopropanes **1d** (4-NO_2) and **1e** (5-NO_2) the transformation proceeded in a more complex manner. Though the formation of nitronate **3da** was observed in 30% yield, its isolation was complicated by decomposition on silica gel. For cyclopropane **1e** bearing a nitro group *para* to bromine, a complex mixture of products was formed which did not include target nitronate **3ea**. Probably, this could be attributed to the increased stability of the palladated species, thus resulting in the possibility of different side reactions. 6-Fluorosubstituted cyclopropane **1f** gave the

corresponding nitronate **3fa** in 59% yield without additional problems.

Surprisingly, 2-(1-bromonaphthyl)-, 2-(1-bromodihydronaphthyl)- and 1-(2-bromothienyl)-substituted cyclopropanes **1g-i** did not give the expected target products even with higher catalyst loadings and prolonged reaction times, presumably, due to steric hindrance.

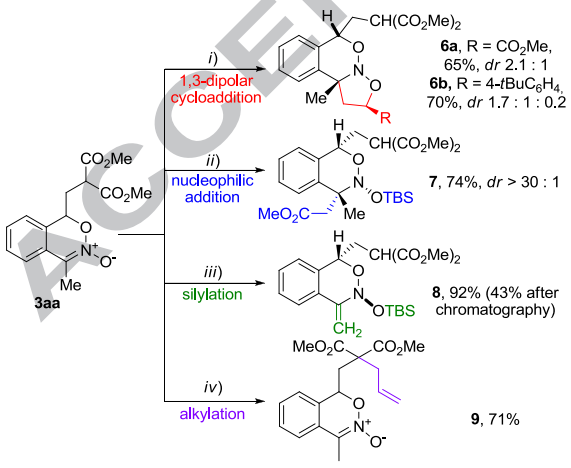
Various nitroalkanes **2b-f** were next introduced to the above-mentioned reaction (Table 2). Although most reacted with bromides **1a-c**, the yields of the corresponding nitronates **3** were lower than that for nitroethane. Probably, the reaction was highly dependent on the steric hindrance of the nitro compound.

The reaction of silylated nitroethanol **2f** (R′ = CH_2OTBS) with cyclopropane **1c** did not proceed due to a rapid β-elimination process. Unfortunately nitro compound **2g** [R′ = $(CH_2)_3CH{=}CHPh$] with a remote alkene function that could provide the corresponding nitronate **3cg**, which would be able to undergo subsequent intramolecular [3+2]-cycloaddition, also failed to undergo the reaction. After 8 hours under the optimized conditions only unreacted cyclopropane **1c** and several by-products from the transformation of reactant **2g** were isolated (for details see ESI, page S23).



Scheme 3. Synthesis of the enantioenriched nitronate (+)-**3ca**.

Additionally it seemed necessary to determine what occurred at the chiral center in the cyclopropane ring of compounds **1** during the formation of nitronates **3**. For this purpose, enantiomerically enriched cyclopropane (−)-**1c** with a (*R*)-configuration of the stereocenter was synthesized by asymmetric carbene addition to 4-methoxy-2-bromostyrene using the Cu(I)/Box system.[14] It was found that the enantiomeric excess of the initial cyclopropane (−)-**1c** was transferred to 2,3-benzoxazine 3-oxide (+)-**3ca** without significant racemization (58% *ee* and 56% *ee*, respectively, Scheme 3).[15,16]



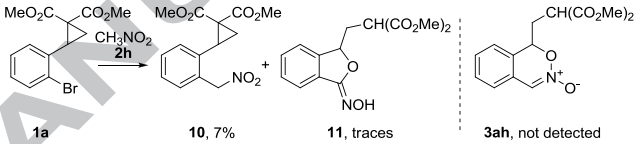
Scheme 4. Chemistry of nitronates **3**. *Reagents and conditions*: *i*) $CH_2{=}CHR$ (2-5 equiv), toluene, reflux, 5-8 h; *ii*) $CH_2{=}C(OMe)OTBS$ (1.3 equiv), TBSOTf (0.2 equiv), CH_2Cl_2, −78 °C, 20 h; *iii*) TBSOTf (1.20 equiv), 2,6-lutidine (1.25 equiv), CH_2Cl_2, −30 °C, 3 h; *iv*) NaH (1.0 equiv), allyl bromide (1.2 equiv), dioxane, r.t. → reflux, 3 h.

The chemistry of benzoxazine *N*-oxides **3** was briefly studied using compound **3aa** (Scheme 4). The tricyclic nitroso acetals **6a,b** were obtained by [3+2]-cycloaddition[8,9] of nitronate **3aa** with methyl acrylate (65%) and *p-tert*-butylstyrene (70%), respectively, by heating at reflux in toluene for 5-8 hours, proceeding with excellent *exo*- but poor facial selectivity.[17]

Nucleophilic addition of a silyl ketene acetal, which was performed at −78 °C,[18] to nitronate **3aa** gave rise to a silylated product **7** as a single diastereomer. Under similar conditions, but utilizing a base instead of a nucleophile,[19] ene-nitroso acetal **8** was obtained.

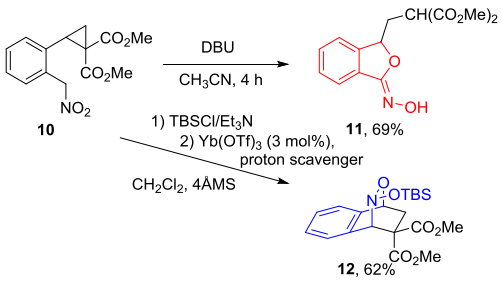
The malonate functional group could also be selectively modified. For example, functionalization of benzoxazine **3aa** with allyl bromide provided allylated benzoxazine **9** in 71% yield.

Finally, we unsuccessfully attempted the preparation of 4-unsubstituted nitronate **3ah** by coupling bromocyclopropane **1a** with nitromethane **2h** (Scheme 5). The reaction rapidly resulted in formation of a palladium mirror leaving cyclopropane **1a** mainly unconsumed, while in the mixture ~7% of non-cyclized product **10** and traces of oxime **11** were detected. Presumably, rapid deactivation of the [Pd] catalyst could be associated with possible carbopalladation of oxime **11**.



Scheme 5. Attempted synthesis of nitronate **3ah** by Pd-coupling. *Reagents and conditions*: nitromethane **2h** (5.0 equiv), $Pd(dba)_2$ (10 mol%), JohnPhos (20 mol%), Cs_2CO_3 (2.0 equiv), dioxane, 75 °C, 30 min; conversion of **1a** ~ 20%.

For better understanding of the failure of this palladium catalyzed coupling, 2-nitromethylphenylcyclopropane **10** was independently synthesized by $AgNO_2$ promoted nucleophilic substitution of the known (2-bromomethylphenyl)cyclopropane.[20] Under basic conditions this was transformed into oxime **11** with the best result obtained using DBU (Scheme 5). For the formation of compound **11**, initial generation of nitronate **3ah** could be postulated and its further rapid rearrangement *via* a nitrile oxide (see ESI, (S34) for details).[21] At the same time, complex benzoxazine scaffold **12** could be assembled from nitro compound **10** by its conversion into silyl nitronate and further intramolecular formal [3+3]-cycloaddition (Scheme 6).[22]



Scheme 6. Attempted assembly of oxazine structures from 2-nitromethylphenyl-cyclopropane **10**.

In summary, we have developed a straightforward method for the synthesis of previously unknown benzannulated six-membered cyclic nitronates **3** from 2-bromoaryl substituted cyclopropanes **1** and primary aliphatic nitro compounds **2**. The tandem reaction is performed using a palladium catalyst and a bulky phosphine ligand.

Acknowledgments

This work was supported by the Russian Science Foundation (Grant 14-50-00126).

Supplementary Data

Crystallographic data for the structures **1b**, **1e**, (−)-**1c**, *trans*-**6a** and **12** have been deposited with the Cambridge Crystallography Data Centre (CCDC# 1416098, 1416099, 1416097, 1416101 and 1416100, respectively). Supplementary data (experimental details, compound characterization, copies of NMR spectra and HPLC) associated with this article can be found in the online version at ….

References and notes

1. For reviews, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151-1196; (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321-347; (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051-3060. (d) Lebold, T. P.; Kerr, M. A. *Pure Appl. Chem.* **2010**, *82*, 1797-1812, (e) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun*. **2011**, *21*, 293-301; (f) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523; (g) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev*. **2014**, *43*, 804-818; (h) Novikov, R. A.; Tomilov, Yu. V. *Mendeleev Commun.* **2015**, 25, 1-10.
2. Selected recent examples of stereodivergent azide addition: (a) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem*. **2012**, *77*, 6634-6637; (b) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Ya. *Chem. Eur. J.* **2015**, *21*, 4975-4987; (c) radicals also could add: Ieki, R.; Kani, Y.; Tsunoi, S.; Shibata, I. *Chem. Eur. J.* **2015**, 6295-6300.
3. Selected recent examples: (a) Hashimoto, T.; Kawamata Y.; Maruoka, K. *Nat. Chem.* **2014**, *6*, 702-705; (b) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. *Org. Lett*. **2014**, *16*, 4896-4899; (c) Tabolin, A. A.; Novikov, R. A.; Khomutova, Yu. A.; Zharov, A. A.; Stashina, G. A.; Nelyubina, Yu. V.; Tomilov, Yu. V.; Ioffe, S. L. *Tetrahedron Lett.* **2015**, *56*, 2102-2105; (d) Wang, H.-P.; Zhang, H.-H.; Hu, X.-Q.; Xu, P.-F.; Luo, Y.-C. *Eur. J. Org. Chem.* **2015**, 3486–3494; (e) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 8006-8009; (f) Ma, W.; Fang, J.; Ren, J.; Wang, Z. *Org. Lett.* **2015**, *17*, 4180–4183.
4. (a) Volkova, Yu. A.; Budynina, E. M.; Kaplun, A. E.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Rybakov, V. B.; Trushkov, I. V.; Melnikov, M. Ya. *Chem. Eur. J.* **2013**, *19*, 6586-6590; (b) Rakhmankulov, E. R.; Ivanov, K. L.; Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Latyshev, G. V.; Trushkov, I. V.; Melnikov, M. Ya. *Org. Lett.* **2015**, *17*, 770-773.
5. (a) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Ya. *J. Org. Chem.* **2011**, *76*, 8852−8868; (b) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov Yu. V. *Angew. Chem. Int. Ed*. **2014**, *53*, 3187–3191.
6. Ono, N.; *The Nitro Group in Organic Synthesis*, Wiley-VCH: Weinheim, 2001; 372 pp.
7. (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360-1370; (b) Vogl, E. M;. Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106-111; (c) Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wife, R. *Tetrahedron Lett.* **2002**, *43*, 2539–2542; (d) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783–11803; (e) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 760–763; (f) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086–4089; (g) Walvoord, R. R.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 8859−8864; (h) Xu, J.; Li, X.; Wu, J.; Dai, W.-M. *Tetrahedron* **2014**, *70*, 3839-3846; (i) Xu, J.; Li, X.; Wu, J.; Dai, W.-M. *Tetrahedron* **2014**, *70*, 6384-6391.
8. a) Denmark, S. E.; Thorarensen, A. *Chem. Rev*. **1996**, *96*, 137-165; b) Baiazitov, R. Y.; Denmark, S. E. "Tandem [4+2]/[3+2] Cycloadditions" In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, 1st ed. Nishiwaki, N. Ed.; John Wiley & Sons, Hoboken, 2014; pp 471-550; c) Seebach, D.; Lyapkalo, I. M.; Dahinden, R.; *Helv. Chim. Acta* **1999**, *82*, 1829–1842.
9. Ioffe, S.L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, 2nd ed. Feuer, H. Ed.; John Wiley & Sons, Chichester, 2008; pp 435-748.
10. Creech, G. S.; Kwon, O.; *J. Am. Chem. Soc.* **2010**, *132*, 8876-8877.
11. Henry, C. E.; Kwon, O.; *Org. Lett.* **2007**, *9*, 3069-3072.
12. (a) Gololobov, Yu. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609−2651; (b) Goudreau, S. R.; Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 470-473; (c) Gonzalez-Bobes, F. Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant M. *Adv. Synth. Catal.* **2008**, *350*, 813-816; (d) for universal syntheses of starting 2-bromoaldehydes, see Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F. *J. Org. Chem.* **2011**, *76*, 6414-6420.
13. Five- and seven-membered homologues of nitronates **3** are known: (a) Boulton, A. J.; Tsoungas, P. G. *J. Chem. Soc. Chem. Commun.* **1980**, 421-422; (b) Boulton, A. J.; Tsoungas, P. G.; Tsiamis, C. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1665-1667; (c) Boulton, A. J.; Tsoungas, P. G.; Tsiamis, C. *J. Chem. Soc. Perkin Trans. 1* **1987**, 695-697; (d) Keumi, T.; Matsuura, K.; Nakayama, N.; Tsubota, T.; Morita, T.; Takahashi, I.; Kitajima, H. *Tetrahedron* **1993**, *49*, 537-556.
14. (a) Marcoux, D.; Goudreau, S. R.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8939-8955. For selected syntheses of chiral 1,1-cyclopropane dicarboxylates, see: (b) Doyle, M. P.; Hu, W. ARKIVOC **2003**, *vii*, 15-22; (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, 130, 8642-8650; (c) Deng, C.; Wang, L.-J.; Zhu, J.; Tang, Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 11620-11623, and references therein.
15. For the probable configuration of benzoxazine (+)-**3ca** and the origins of chirality transfer, see ESI (page S25).
16. For previous attempts regarding the catalytic enantioselective synthesis of six-membered cyclic nitronates (without chiral auxiliaries), see ref. 8c and references therein.
17. In contrast to the data obtained in this paper, coumarine-annulated nitronates (see ref 11) have shown excellent facial selectivity in [3+2]-cycloaddition. For discussion about the selectivity of [3+2]-cycloaddition for nitronates **3** and related compounds see ESI (page S31).
18. (a) Smirnov, V. O.; Ioffe, S. L.; Tishkov, A. A.; Khomutova, Yu. A.; Nesterov, I. D.; Antipin, M. Y.; Smit, W. A.; Tartakovsky, V. A. *J. Org. Chem*. **2004**, *69*, 8485-8488; (b) Naumova, A. S.; Mikhaylov, A. A.; Khomutova, Yu. A.; Struchkova, M. I.; Ioffe, S. L.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2012**, 2219–2224.
19. Tishkov, A. A.; Lesiv, A. V.; Khomutova, Yu. A.; Strelenko, Yu. A.; Nesterov, I. D.; Antipin, M. Y.; Ioffe, S. L.; Denmark, S. E. *J. Org. Chem.* **2003**, *68*, 9477-9480.
20. Dias, D. A.; Kerr, M. A. *Org. Lett*. **2009**, *11*, 3694-3697.
21. Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306-1307.
22. Mikhaylov, A. A.; Novikov, R. A.; Khomutova, Yu. A.; Arkhipov, D. E.; Korlyukov, A. A.; Tabolin, A. A.; Tomilov, Yu. V.; Ioffe, S. L. *Synlett* **2014**, *25*, 2275-2280.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Tandem Pd-catalyzed C-C coupling/recyclization of 2-(2-bromoaryl)cyclopropane-1,1-dicarboxylates with primary nitro alkanes

Leave this area blank for abstract info.

Andrey A. Mikhaylov, Alexander D. Dilman, Roman A. Novikov, Yulia A. Khoroshutina, Marina I. Struchkova, Dmitry E. Arkhipov, Yulia V. Nelyubina, Andrey A. Tabolin, Sema L. Ioffe