Mendeleev Communications

Mendeleev Commun., 2027, **37**, in press

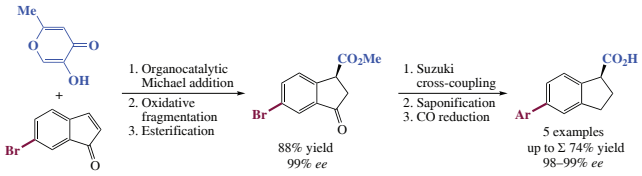
Organocatalytic access to 5-bromo-3-oxoindane-1-carboxylate enantiomers, good cross-components for the Suzuki coupling

Madina Zhanabaeva, Ruslan A. Kovalevsky, Andrey N. Komogortsev, Andrei A. Vasil'ev, Alexander S. Kucherenko* and Sergei G. Zlotin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: alexkucherenko@yandex.ru; zlotin@ioc.ac.ru

DOI: 10.71267/mencom.8177

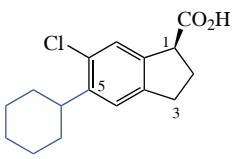
The enantiodivergent Michael addition of allomaltol to 6-bromoinden-1-one assisted by either cinchonidine–squaramide or cinchonine–squaramide hybrid organocatalysts affords the *S*- or *R*-configured adducts, respectively; the transformation of the allomaltol moiety in the *S*-adduct affords the key methyl (1*S*)-5-bromo-3-oxoindane-1-carboxylate with 99% *ee*. The subsequent Suzuki–Miyaura cross-coupling, saponification and the Clemmensen reduction proceed with no loss in the *ee* value and provide a series of (1*S*)-5-arylindane-1-carboxylic acids. When arylboronic acid contains additional azido group, the cross-coupling product is suitable for the copper(I)-catalyzed cycloaddition with alkynes.



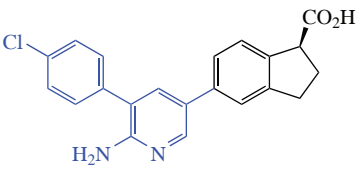
Keywords: asymmetric organocatalysis, Michael addition, post-functionalization, Suzuki–Miyaura cross-coupling, click reaction, chiral indanecarboxylic acids.

Chiral indane-1-carboxylic acids bearing 5-positioned substituents are known to exhibit various biological activities.[1,2] The well-known drug Clidanac, whose molecule contains cyclohexyl group, would block oxidative phosphorylation processes in animals and is used as an anti-inflammatory agent for treatment of rheumatoid arthritis.[3] Aminopyridinyl-substituted indanecarboxylic acid can inhibit mitogen-activated protein kinase 4 (MAP4K4), with the (*S*)-enantiomer being ten times more active than its (*R*)-antipode.[4] (*R*)-Configured anticoagulant Camonagrel is known to selectively inhibit platelet thromboxane synthase.[5]

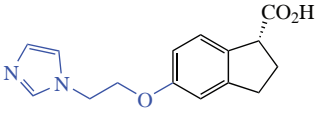
However, the documented syntheses of non-racemic 5-substituted indane-1-carboxylic acids are scarce. Separation of racemates using chiral auxiliaries or HPLC on chiral columns is obviously impractical.[6] Recently,[7] Tang reported on asymmetric hydrocarboxylation of indenes with carbon dioxide employing Ni^{II}/SaBOX (15 mol%) catalytic system and manganese metal (3 equiv.) as the principal reductant. Although the regioselectivity of the reaction was moderate (the ratio between 1- and 2-carboxy isomers varied from 3.7 : 1 to 5.9 : 1), the *ee* values for each regioisomer approached 86–96%.



(*S*)-Clidanac



MAP4K4 inhibitor



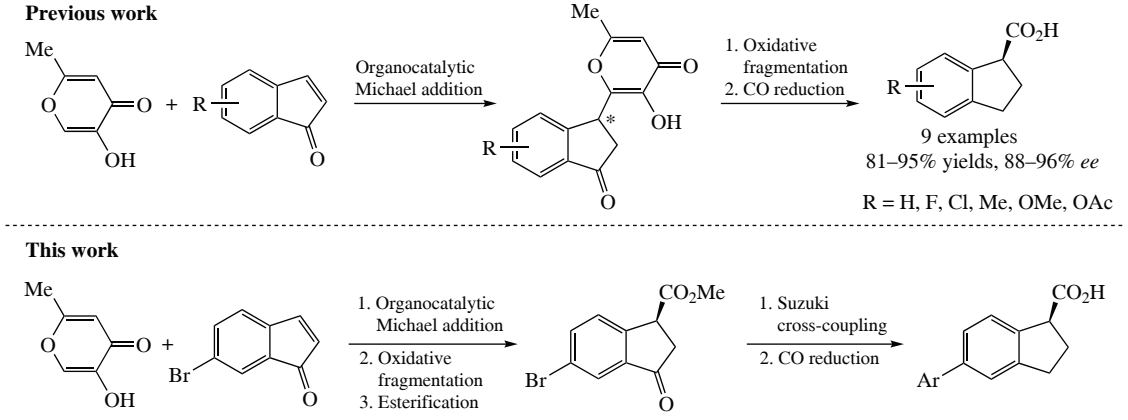
(*R*)-Camonagrel

Recently,[8] we have developed the synthesis of enantiopure indane-1-carboxylic acids involving organocatalytic Michael addition of allomaltol to oxoindenes followed by the oxidative fragmentation of the allomaltol part into carboxy group (Scheme 1, top). The organocatalytic step was promoted by special hybrid compounds containing chiral alkaloid and squaramide moieties (Figure 1, *e.g.*, structure **OC1**), and inexpensive allomaltol served as the synthetic equivalent for carboxy group. The final Clemmensen reduction of the oxo group afforded the target products in 81–95% overall yields and with *ee* values up to 96%.

Despite these recent advances, general catalytic enantioselective approaches to a broad variety of 5-substituted indane-1-carboxylic acids remain underexplored. Herein, we propose the promising extension of our previous finding[8] of the Michael reaction between allomaltol and oxoindenes when the oxoindene counterpart contains bromine atom in the proper position (see Scheme 1, bottom). The bromoarene moiety of the thus accessed 5-bromo-3-oxoindane-1-carboxylate looks good for transition metal cross-couplings, in particular, the Suzuki–Miyaura reaction. The presence of additional functional groups in the arylboronic acids utilized may allow for some further post-modifying of the cross-coupling products.

In our previous work,[8] the substrate scope was studied using the optimization results found for model unsubstituted oxoindene (see Scheme 1, top, R = H, for which the best organocatalyst was **OC1**). However, for some substrates the optimal conditions may differ from those selected for the model. Therefore, we decided

© 2027 Mendeleev Communications



Scheme 1

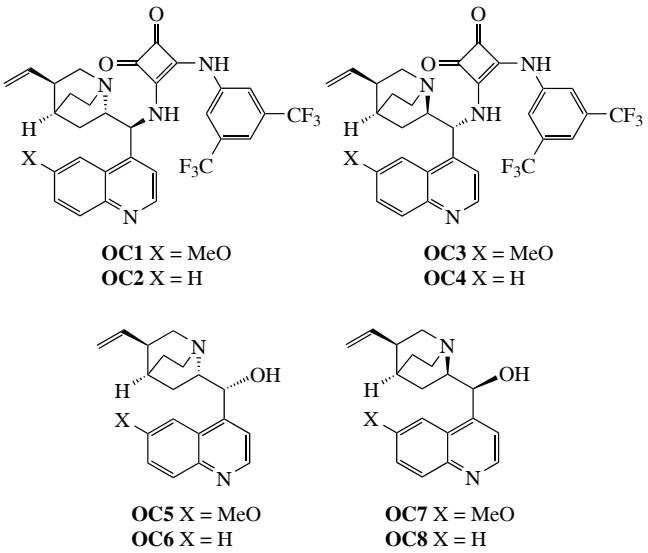
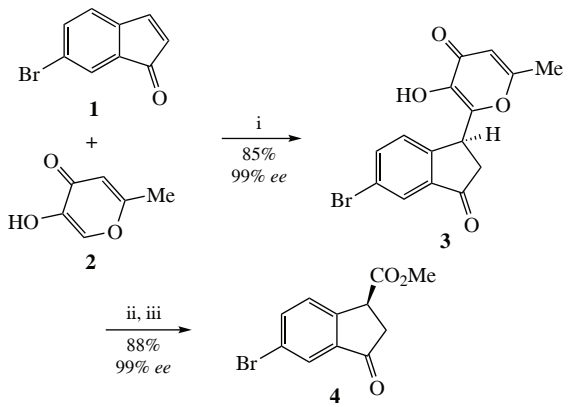


Figure 1 Selected organocatalysts for the asymmetric Michael addition reaction.

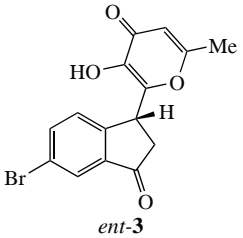
to re-optimize the conditions for reaction between the particular 6-bromoinden-1-one **1** and allomaltol **2** to produce the Michael adduct **3** (Scheme 2). The screening of bifunctional tertiary amines **OC1**–**OC4** and native alkaloids **OC5**–**OC8** (see Figure 1, *cf.* refs. 8, 9) was performed under model conditions (CH_2Cl_2, catalyst loading 10 mol%, ~20 °C, 24 h, Table 1, entries 1–8). When catalysts **OC1**, **OC2**, **OC5**, **OC6** were applied (entries 1, 2, 5, 6), the product had (*S*)-configuration,[8] whereas in cases of pseudo-epimeric catalysts **OC3, OC4**, **OC7**, **OC8**, the product was expectedly (*R*)-configured (entries 3, 4, 7, 8). Diastereomeric squaramide catalysts based on quinine (**OC1**) and quinidine (**OC3**) both provided high stereoinduction (94 and –92% *ee*, respectively) and product yields (entries 1, 3). Surprisingly, squaramide catalysts based on cinchonidine (**OC2**) and cinchonine (**OC4**) (not optimal for bromine-free analog[8]) turned out to be even better in case of bromo derivative **1** (99 and –95% *ee* values, respectively, entries 2, 4). The use of the initial natural alkaloids **OC5**–**OC8** lacking the squaramide grouping gave product with low *ee* values and moderate yields (entries 5–8).



Scheme 2 *Reagents and optimal conditions*: i, **1** and **2** (5 mmol each), organocatalyst **OC2** (10 mol%), CH_2Cl_2, room temperature, 24 h; ii, $RuCl_3 \cdot H_2O$ (1 mol%), $NaIO_4$ (10 equiv.), $MeCN/CCl_4/H_2O$ (2 : 2 : 5); iii, MeOH, H_2SO_4 (cat.).

Then, the **OC2**-catalyzed reaction **1**+**2** was tested in other aprotic (PhMe, MeCN, THF) or protic solvents (EtOH or H_2O); however, these results were inferior (entries 9–13). Reduction of catalyst loading to 5% or performing the reaction at 5 °C noticeably decelerated the process with slight diminishing the enantioselectivity (see entry 2; for details of the stereoinduction mechanism, see Online Supplementary Materials, Scheme S1).

The **OC2**-catalyzed reaction between compounds **1** and **2** turned out to be good for scaling. The 5 mmol loading of the reactants provided product **3** in 1.42 g (85%) yield and with 99% *ee* value. The next oxidative fragmentation of the allomaltol moiety in **3** followed by esterification of the intermediate carboxylic acid afforded analytically pure bromo oxo ester **4** (0.99 g, 88%, 99% *ee*). Antipode *ent*-**3** was also prepared (82% yield, 95% *ee*) in a larger scale when pseudo-enantiomeric catalyst **OC4** was applied. Enantiomeric purity of substance *ent*-**3** was improved to 99% upon its additional recrystallization from isopropanol (see Table 1, entry 4), the yield of purified *ent*-**3** having been 68%.

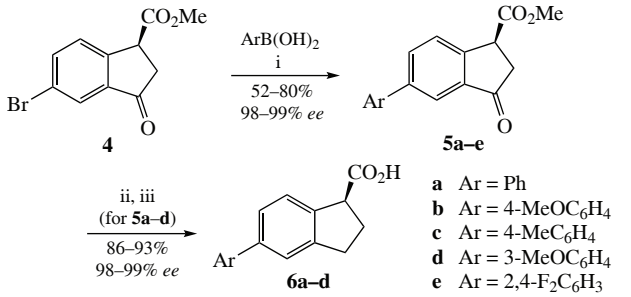


Bromoarene ester **4** was then subjected to the Suzuki–Miyaura cross-coupling with some arylboronic acids under classical conditions (Scheme 3). Generally, the yields of products **5a**–**d** were good (63–80%), while in case of less nucleophilic 2,4-difluorophenylboronic acid the yield of biaryl **5e** was 52%. Enantiomeric purity of all compounds **5a**–**e** was 98–99% *ee*, so heating under basic (Na_2CO_3) conditions did not cause epimerization at position 1. Saponification of methyl esters **5a**–**d** with $LiOH \cdot H_2O$ followed by the Clemmensen reduction of the oxo group afforded the target 5-arylindane-1-carboxylic acids **6a**–**d** with high overall yields and full preservation of the enantiomeric purity.

Table 1 Optimization of the enantioselective Michael addition of allomaltol **2** to 6-bromoinden-1-one **1**.[a]

Entry	Organo-catalyst	Solvent	Product **3** or *ent*-**3**		
			Yield[b] (%)	Confi-guration	*ee* value[c] (%)
1	**OC1**	CH_2Cl_2	80	*S*	94
2	**OC2**	CH_2Cl_2	85 (60,[d] 56[e])	*S*	99 (97,[d] 98[e])
3	**OC3**	CH_2Cl_2	82	*R*	–92
4	**OC4**	CH_2Cl_2	82	*R*	–95
5	**OC5**	CH_2Cl_2	36	*S*	12
6	**OC6**	CH_2Cl_2	36	*S*	15
7	**OC7**	CH_2Cl_2	40	*R*	–20
8	**OC8**	CH_2Cl_2	38	*R*	–16
9	**OC2**	PhMe	82	*S*	75
10	**OC2**	MeCN	30	*S*	91
11	**OC2**	THF	27	*S*	95
12	**OC2**	EtOH	15	*S*	8
13	**OC2**	H_2O	–	–	–

[a] Organocatalyst **OC1**–**OC8** (10 mol%), oxoindene **1** (20.9 mg, 0.1 mmol), allomaltol **2** (12.6 mg, 0.1 mmol), solvent (0.5 ml), room temperature. [b] Yield of **3** was determined after filtration through silica gel and evaporation of the solvent. [c] From HPLC on the chiral phase (CHIRALPAK AD-H column, *n*-hexane/PrⁱOH 70 : 30, flow rate 1.00 ml min^{-1}, 220 nm detector; t_1 = 8.7 min, t_2 = 10.2 min). [d] With 5.0 mol% of **OC2**. [e] At 5 °C.

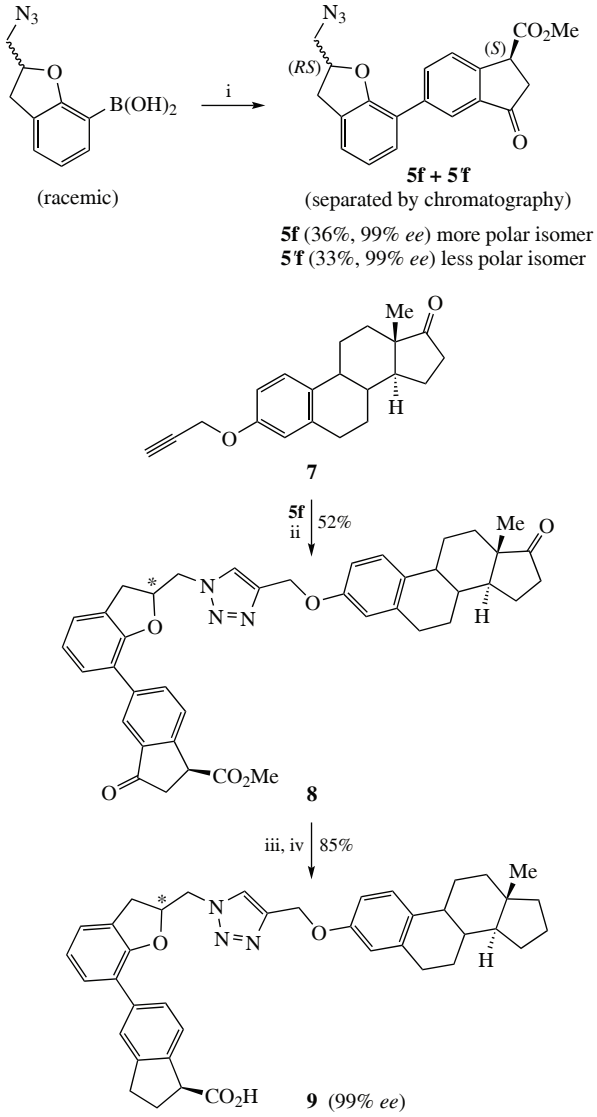


Scheme 3 *Reagents and conditions*: i, $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, H_2O, 80 °C, 8 h; ii, $LiOH \cdot H_2O$, dioxane/MeCN/H_2O, 0 °C, 2 h; iii, Zn/Hg, PhMe, HCl (aq.), reflux, 6 h.

We also utilized a more sophisticated arylboronic acid incorporating fused 2-azidomethyldihydrofuran core[10] aiming to obtain a more complex derivative **5f** (Scheme 4). Since the sample of this boronic acid containing chiral center was racemic, the cross-coupling brought about the mixture of two diastereomers **5f** and **5′f** in approximately equal amounts. To our delight, these diastereomers were well separable by column chromatography and their enantiomeric purities were as high as 99% *ee*. To our disappointment, none of them was crystalline to employ X-ray for determination configuration, whereas their NMR properties were expectedly close as the chiral centers in them were remote enough. We are looking forward how to solve this challenging task for deduction of their true configuration.

Anyway, we decided to perform the Cu-catalyzed cycloaddition of one of the azido-substituted compounds and chose at random more polar diastereomer **5f**. With *O*-propargylated estrone **7**[11] as the alkyne component, the cycloaddition led to the desired 1,2,3-triazole derivative **8** in 52% yield (see Scheme 4). Hydrolysis of the ester group in it with $LiOH \cdot H_2O$ followed by the Clemmensen reduction (both oxo groups underwent the transformation) gave product **9** with 85% yield and enantiopurity remained at the 99% *ee* level. This example may be challenging for the asymmetric synthesis of various carboxyindane–steroid hybrids interesting in view of 'twin drug' concept.[12–15]

In conclusion, we have developed an efficient strategy for enantioselective organocatalytic synthesis of chiral 5-substituted indane-1-carboxylic acids based on the asymmetric addition of



Scheme 4 *Reagents and conditions*: i, bromoarene **4**, $Pd(PPh_3)_4$, Na_2CO_3, PhMe, H_2O, 80 °C, 8 h; ii, azide **5f**, CuI (2 mol%), DIPEA (4 mol%), AcOH (4.5 mol%), CH_2Cl_2; iii, $LiOH \cdot H_2O$, dioxane/MeCN/H_2O, 0 °C, 2 h; iv, Zn/Hg, PhMe, HCl (aq.), reflux, 6 h.

allomaltol to 6-bromoinden-1-one. The post-functionalization of the Michael adducts including oxidative fragmentation and the Suzuki–Miyaura cross-coupling at the bromoarene part affords a series of 5-arylindane-1-carboxylic acids with good yields and excellent (~99% *ee*) enantioselectivity, with the method being suitable for the preparation of both enantiomeric forms. When the arylboronic acid contains an extra azido group, the cross-coupling product can be further involved in the copper(I)-catalyzed click reaction; this strategy may provide access to a range of hybrid compounds containing two bioactive parts in one molecule, which conforms with the 'twin drugs' concept.

This work was supported by The Russian Science Foundation (grant no. 23-13-00250-P).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8177.

References

1 P. Prasher and M. Sharma, *ChemistrySelect*, 2021, **6**, 2658; https://doi.org/10.1002/slct.202100177.

2 G. R. Allen, R. Littell, F. J. McEvoy and A. E. Sloboda, *J. Med. Chem.*, 1972, **15**, 934; https://doi.org/10.1021/jm00279a014.

3 K. Kawai, H. Shiojiri, H. Fukushima, Y. Nozawa, J. Hasegawa, M. Nozaki, K. Tsurumi and H. Fujimura, *Res. Commun. Chem. Pathol. Pharmacol.*, 1984, **45**, 399; https://popline.org/node/230586.
4 M. Zhanabaeva, R. A. Kovalevsky, A. S. Kucherenko, A. A. Korlyukov and S. G. Zlotin, *Org. Biomol. Chem.*, 2025, **23**, 5611; https://doi.org/10.1039/d5ob00551e.
5 M. A. Villalobos, J. P. de la Cruz, R. Escalante, M. M. Arrebola, A. Guerrero and F. Sánchez de la Cuesta, *Pharmacology*, 2003, **69**, 44; https://doi.org/10.1159/000071266.
6 S. Noguchi, S. Kishimoto, I. Minamida and M. Obayashi, *Chem. Pharm. Bull.*, 1974, **22**, 529; https://doi.org/10.1248/cpb.22.529.
7 L. Zhou, L. Li, S. Zhang, X.-K. Kuang, Y.-Y. Zhou and Y. Tang, *J. Am. Chem. Soc.*, 2024, **146**, 18823; https://doi.org/10.1021/jacs.4c05217.
8 M. Zhanabaeva, A. A. Korlyukov, R. A. Kovalevsky, A. S. Kucherenko and S. G. Zlotin, *Org. Biomol. Chem.*, 2025, **23**, 5611; https://doi.org/10.1039/d5ob00551e.
9 E. Paradisi, P. Righi, A. Mazzanti, S. Ranieri and G. Bencivenni, *Chem. Commun.*, 2012, **48**, 11178; https://doi.org/10.1039/c2cc35582e.
10 S. I. Sviridov, A. A. Vasil'ev, N. L. Sergovskaya, M. V. Chirskaya and S. V. Shorshnev, *Tetrahedron*, 2006, **62**, 2639; https://doi.org/10.1016/j.tet.2005.12.026.
11 P. Ramírez-López, M. C. de la Torre, H. E. Montenegro, M. Asenjo and M. A. Sierra, *Org. Lett.*, 2008, **10**, 3555; https://doi.org/10.1021/ol801313g.
12 J. Szabó, Z. Pataki, J. Wölfling, G. Schneider, N. Bózsity, R. Minorics, I. Zupkó and E. Mernyák, *Steroids*, 2016, **113**, 14; https://doi.org/10.1016/j.steroids.2016.05.010.
13 R. Jójárt, P. Traj, É. Kovács, Á. Horváth, G. Schneider, M. Szécsi, A. Pál, G. Paragi and E. Mernyák, *Molecules,* 2019, **24**, 1783; https://doi.org/10.3390/molecules24091783.
14 M. Patra and G. Gasser, *Nat. Rev. Chem.*, 2017, **1**, 0066; https://doi.org/10.1038/s41570-017-0066.
15 R. Wang, H. Chen, W. Yan, M. Zheng, T. Zhang and Y. Zhang, *Eur. J. Med. Chem.*, 2020, **190**, 112109; https://doi.org/10.1016/j.ejmech.2020.112109.

Received: 18th August 2026; Com. 26/8177

Contents entry

Organocatalytic access to 5-bromo-3-oxoindane-1-carboxylate enantiomers, good cross-components for the Suzuki coupling

Madina Zhanabaeva, Ruslan A. Kovalevsky, Andrey N. Komogortsev, Andrei A. Vasil'ev, Alexander S. Kucherenko, Sergei G. Zlotin

