VIP *Very Important Paper*

Time-Economical Synthesis of Diarylacetates Enabled by TfOH-Catalyzed Arylation of α-Aryl-α-Diazoesters with Arenes

Sha Hu,[a, b] Jiale Wu,[a, b] Zuolin Lu,[c] Jiaqi Wang,[a, b] Yuan Tao,[a, b] Meifen Jiang,*[a, b] and Fener Chen*[a, b, c]

Diarylacetates are privileged structures of many bioactive natural products and pharmaceutical compounds. A time-economical synthesis of diarylacetates by TfOH-catalyzed arylation of α-aryl-α-diazoesters with arenes is described. This protocol provides a variety of diarylacetates in good yields with broad substrate scope, excellent functional group compatibility, and mild reaction conditions. Also, a new mechanism for the arylation reaction of α-aryl-α-diazoesters with arenes under TfOH catalysis is presented.

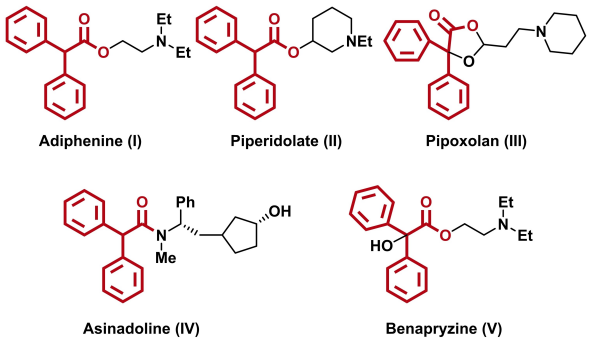


Figure 1. Selected Biologically Active Diarylacetate Derivatives.

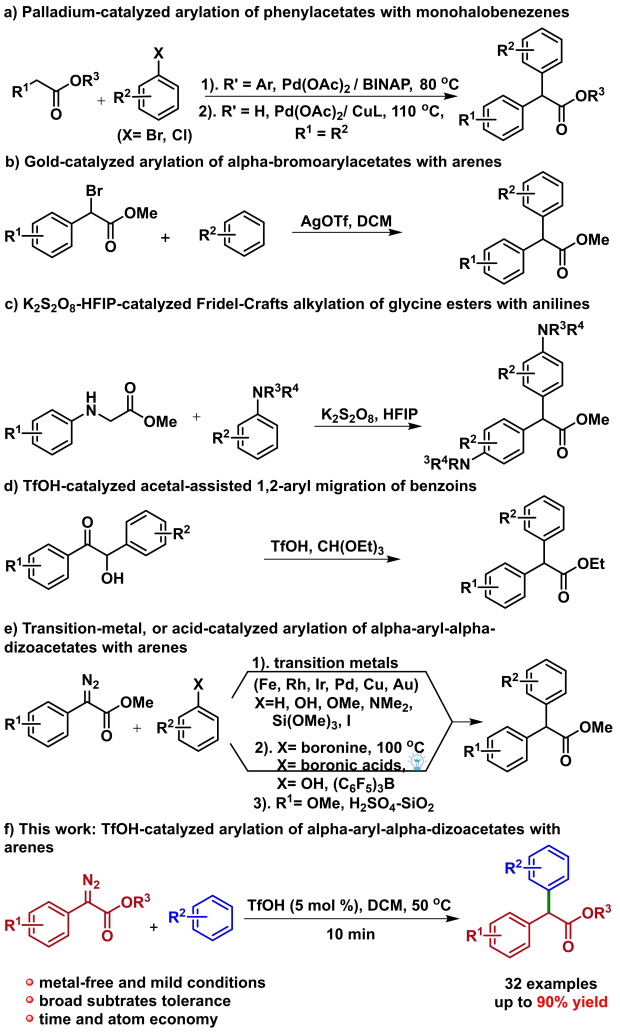
Diarylacetates are prominent scaffolds in natural products, pharmaceuticals, and building blocks of complex molecules (Figure 1).[1] For example, anti-cholinergic drugs, adiphenine (**I**),[2] piperidolate (**II**),[3] and pipoxolan (**III**),[4] are used clinically to relieve smooth muscle hypermotility and spasms. At the same time, Pipoxolan (**III**) also inhibits the proliferation of human lung cancer cells (CL 1–5), tumor cells, and leukemia cells (HL-60, U937, and K-562). Asimadoline (**IV**),[5] a potent k-opioid receptor agonist, reduces sensation to colonic distension and irritable bowel syndrome. Benapryzine (**V**),[6] an anti-Parkinson's drug, inhibits dopamine absorption into corpus striatum *in vitro*. Therefore, the development of diverse strategies for the synthesis of diarylacetate derivatives is of great significance as a result of their versatile pharmacological activities and their utility in drug discovery.

Traditionally, diarylacetate derivatives have been synthesized by the Pd-catalyzed α-arylation of phenyl- and ethyl-acetates with monohalobenzenes,[7] the Friedel-Crafts alkylation of α-bromoarylacetates with arenes in the presence of AgOTf,[8] the double Friedel-Crafts alkylation of glycine esters with anilines using $K_2S_2O_8$-HFIP,[9] and the *in-situ* generated acetal-assisted 1,2-aryl migration of benzoins under TfOH catalysis (Scheme 1, a–d).[10] However, these processes suffer from many drawbacks such as not easy available or not readily prepared materials, harsh reaction conditions, and functional group incompatibility, *etc.* Thus, developing a straightforward synthetic procedure that can overcome these challenges is needed. In recent years, diazo compounds are remarkably versatile and useful building blocks for an array of chemical transformations in organic synthesis.[11] In particular, a few research groups have reported the efficient synthesis of diarylacetates by the carbene transfer reactions of α-aryl-α-diazoesters with arenes using transition metals (Fe,[12] Rh,[13] Ir,[14] Pd,[15] Cu,[16] and Au,[17]) (Scheme 1, e1). Despite these advances, they all have limitations, such as the use of toxic transition-metal catalysts and the requirement of using arenes with activated substituents (OH, OMe, NMe_2, $Si(OMe)_3$, and I). Wang group and Jurberg group independently achieved the metal-free arylation of α-aryl-α-diazoesters with arylboron reagents under basic conditions at 100 °C or blue light, leading to the corresponding diarylacetate products (Scheme 1, e2).[18] Zhang group described $(C_6F_5)_3B$-catalyzed ortho-selective substitution of α-aryl-α-diazoesters with phenols (Scheme 1, e2).[19]

These boron substrates can be expensive and/or require multistep preparation, thus rendering them less practical for larger scale applications. Very recently, Burtoloso and co-workers reported an elegant arylation of α-methoxy-phenyl-α-diazoesters with arenes catalyzed by H_2SO_4–SiO_2 for the synthesis of electron-rich diarylacetates derivatives (Scheme 1, e3).[20] However, in this protocol, only α-methoxy-phenyl-α-

[a] Dr. S. Hu, Dr. J. Wu, Dr. J. Wang, Dr. Y. Tao, Dr. M. Jiang, Prof. F. Chen
Engineering Center of Catalysis and Synthesis for Chiral Molecules
Department of Chemistry
Fudan University
200433 Shanghai (P. R. China)
E-mail: jiang_meifen@fudan.edu.cn
rfchen@fudan.edu.cn
[b] Dr. S. Hu, Dr. J. Wu, Dr. J. Wang, Dr. Y. Tao, Dr. M. Jiang, Prof. F. Chen
Shanghai Engineering Center of Industrial Catalysis for Chiral Drugs
200433 Shanghai (P. R. China)
[c] Z. Lu, Prof. F. Chen
Institute of Pharmaceutical Science and Technology
Zhejiang University of Technology
310014 Hangzhou (P. R. China)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.202100271



Scheme 1. Strategies to Access Diarylacetates.

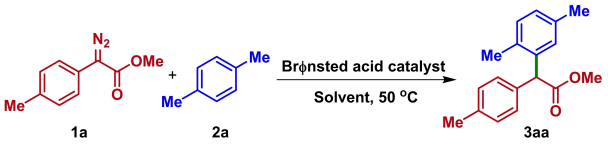
diazoesters and electron-rich arenes, phenols or methoxybenzenes were employed as the substrates.

We recently developed the TfOH-catalyzed N–H insertion[21] of α-aryl-α-diazoesters with anilines, and C–H activation/lactonization of α-aryl-α-diazoesters with phenols, in which diazo compounds would be able to undergo *ortho* C–H insertion with phenolic base nucleophiles.[22] Perceiving the advantages of these approaches that Brønsted acid is very important between diazo compounds and aromatic hydrocarbons, we envisioned that Brønsted acid could be able to expand methods for the preparation of various substituents diarylacetates. Meanwhile, we focus on the economic methods which are mainly driven by the atom economy, step economy, and time economy.[23] Herein, we reported the TfOH-catalyzed time-economical arylation of α- aryl-α-diazoesters with arenes for the synthesis of diarylacetates. This methodology features metal-free mild reaction conditions and demonstrates excellent functional group compatibility. Additionally, we introduced a different mechanism with Burtoloso's work.

We began studying the reaction under our previous reaction conditions for the cascade C–H activation/lactonization of α-aryl-α-diazoacetates with phenols[22] to check whether our established method could be operative toward the arylation of methyl α-(*p*-tolyl)-α-diazoacetate **1a** with *p*-xylene **2a** (Table 1). To our delight, the desired diarylacetate product **3aa** was obtained in 83% yield when 10 mol% of TfOH was used as the catalyst (entry 1). However, switching from TfOH to H_2SO_4 dramatically decreased the yield of **3aa** to less than 10%, and a long reaction time was needed (24 h, entry 2). The use of TsOH, TFA, and MsOH also gave unsatisfied results 35%, 50%, and 43% yields, respectively (entries 3–5). Further solvent screening was examined, the use of other chlorinated solvents such as dichloroethane (DCE) or chloroform ($CHCl_3$) was found to be less effective than dichloromethane (DCM) (entries 6–7). Replacement of DCM with ethyl acetate (AcOEt) gave a poor yield of **3aa** (30%, entry 8). Reactions in acetone or acetonitrile provided trace amounts of product **3aa** (entries 9–10). When decreasing the catalyst loading from 10 mol% to 5 mol%, a similar yield of **3aa** was obtained (entry 11).

With the optimized reaction conditions in hand, the substrate scope of arenes was then investigated, and the results are summarized in Table 2. The unsubstituted benzene proceeded smoothly to give the corresponding product **3ab** in 72% yield. But the arylation reaction using anisole as the substrate under the above optimized reaction conditions afforded an inseparable mixture (3:1) of the regioisomers **3ac-1** and **3ac-2** in a combined yield of 78%. The disubstituted benzene derivatives bearing electron-donating and electron-withdrawing substituents at any of two positions on phenyl ring were tolerant in this reaction, producing the corresponding products **3aa**–**3ad** in good to high yields (60–86%) as a single isomer. The *tri*-substituted benzene derivatives mesitylene and *tetra*-substituted benzene derivatives 1,2,4,5-tetramethylbenzene were suitable substrates to yield **3aj** and **3ak** in 74

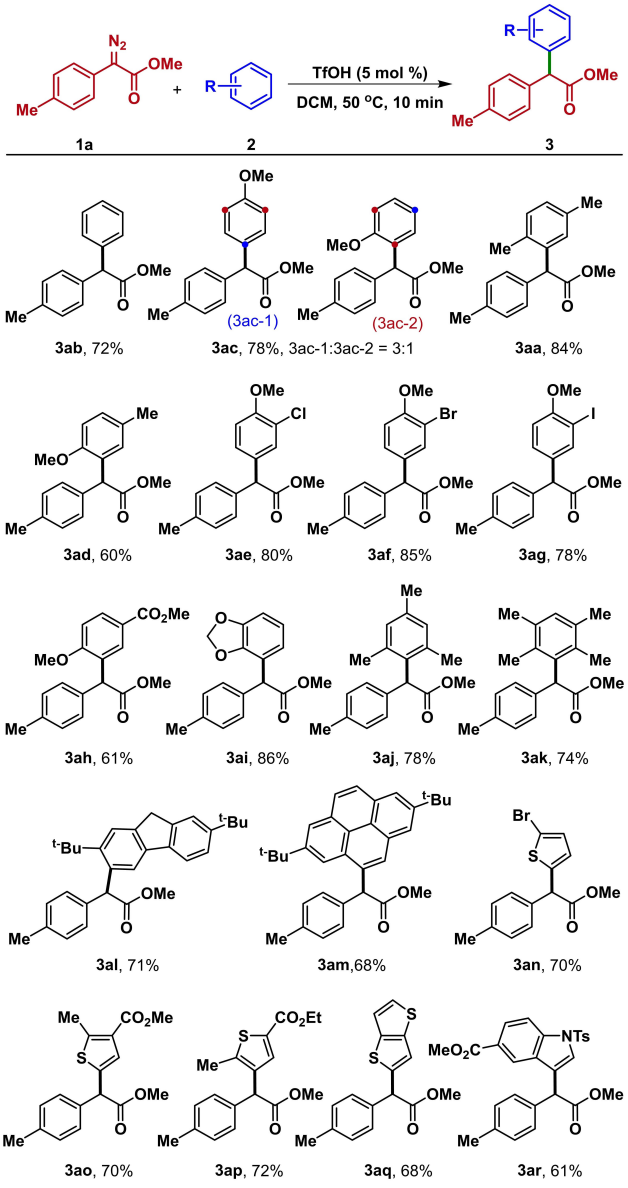
Table 1. Optimization of the Reaction Condition.[a]



Entry	Brønsted acid [mol%]	Solvent	Time[b] [h]	Yield[c] [%]
1	TfOH (10)	DCM	0.17	83
2	H_2SO_4 (10)	DCM	24	<10
3	TsOH (10)	DCM	24	35
4	TFA (10)	DCM	24	50
5	MsOH (10)	DCM	0.17	43
6	TfOH (10)	DCE	0.17	78
7	TfOH (10)	$CHCl_3$	0.17	76
8	TfOH (10)	AcOEt	0.17	30
9	TfOH (10)	Acetone	0.17	trace
10	TfOH (10)	MeCN	0.17	trace
11	TfOH (5)	DCM	0.17	84

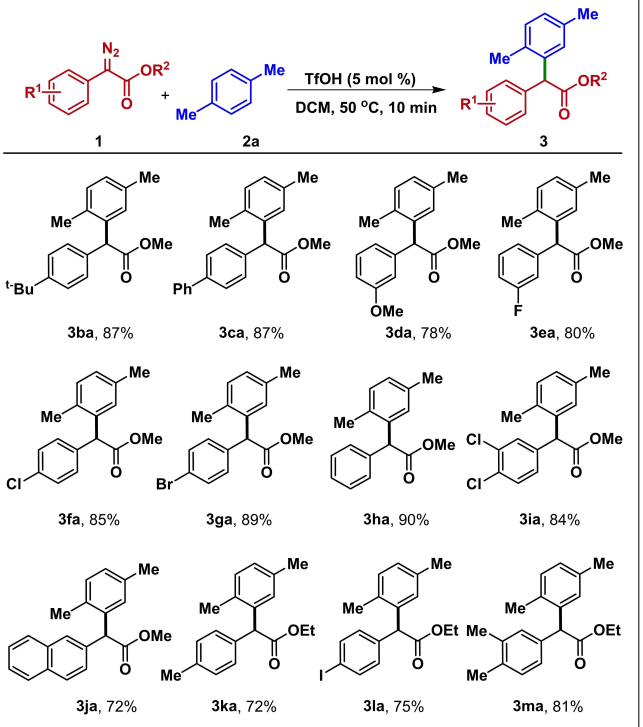
[a] Reaction conditions: methyl α-(*p*-tolyl)-α-diazoacetate **1a** (0.2 mmol, 1.0 equiv), *p*-xylene **2a** (0.2 mmol, 1.0 equiv), and catalyst (mmol%) in the solvent (0.8 ml, 0.25 M) at 50°C under air. [b] Complete conversion reaction time of **1a**. [c] Isolated yield.

Table 2. Substrate Scope of Arenes.[a,b]



[a] Reaction conditions: methyl α-(*p*-tolyl)-α-diazoacetate **1a** (0.2 mmol, 1.0 equiv), arenes **2** (0.2 mmol, 1.0 equiv), and TfOH (5 mmol%) in DCM (0.8 ml, 0.25 M) at 50°C for 0.17 h under air. [b] Isolated yield.

Table 3. Substrate Scope of α-Aryl-α-Diazoacetates.[a,b]

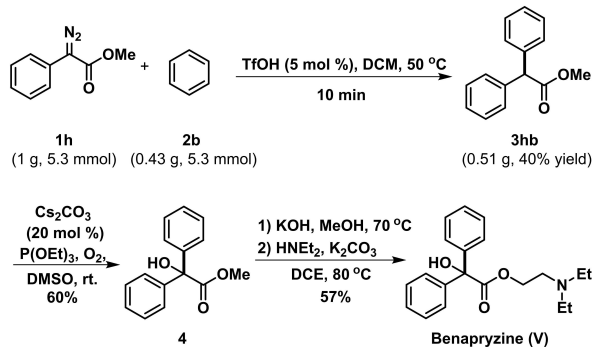


[a] Reaction conditions: α-aryl-α-diazoacetate **1** (0.2 mmol, 1.0 equiv), *p*-xylene **2a** (0.2 mmol, 1.0 equiv), and TfOH (5 mmol%) in DCM (0.8 ml, 0.25 M) at 50°C for 0.17 h under air. [b] Isolated yield.

and 78% yields, respectively. When the phenyl ring was replaced with sterically bulky fluorene or 9*H*-pyrene ring, as expected, the reaction also worked smoothly to cleanly afford the desired products **3al** and **3am** in 71% and 68% yields, respectively. Similarly, the heterocyclic (5-bromothienyl, methyl 4-carboxylate-5-methylthienyl, ethyl 5-carboxylate-2-methylthienyl, thieno[3,2-*b*]thiophenyl, and methyl 5-carboxylate 1-tosyl-1*H*-indolyl) arenes were also effective for this transformation and furnished the corresponding products **3an**–**3ar** in moderate to good yields (61–72%).

Having demonstrated the generality of arenes, we next moved on to examine the scope of α-aryl-α-diazoesters. As illustrated in Table 3, the arylation reaction of mono-substituted methyl α-phenyl-α-diazoesters bearing electron-donating (methyl, *tert*-butyl, phenyl, and methoxy) and electron-withdrawing (fluoro, chloro, and bromo) at any of the positions of phenyl ring were all reacted smoothly to furnish the corresponding diarylacetate products **3aa**–**3ga** in very good yields. Remarkably, the unsubstituted benzene proved to be an excellent substrate for this reaction, giving the diarylacetate product **3ha** in 90% yield. A disubstituted methyl α-aryl-α-diazoester could be also tolerated under the standard conditions to afford the arylation product **3ia** in 84% yield. In addition to methyl α-phenyl-α-diazoacetates, methyl α-2-naphthyl-α-diazoacetate was also cleanly transformed into the corresponding product **3ja** in 72% yield. Gratifyingly, varying the methyl ester group into ethyl ester group was also suitable to this reaction, and giving the desired arylation products **3ka**–**3ma** in 72–81% yields.

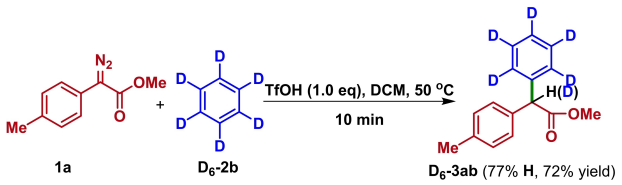
To further evaluate the efficacy and synthetic utility of this methodology, we carried out the scale-up experiment using 5.3 mmol (1.0 g) of methyl α-phenyl-α-diazoacetate and 5.3 mmol (0.43 g) of benzene under the optimal reaction conditions, which provided the desired product methyl diphenylacetate **3hb** in 40% yield (Scheme 2).[18a] The diphenylacetate **3hb** is a key intermediate for the preparation of antiparkinsonian drug benapryzine (**V**), which was derived from **3hb** according to the protocol developed by Jurberg (C–H hydroxylation followed by the hydrolysis **3hb** as well as *O*-alkylation).



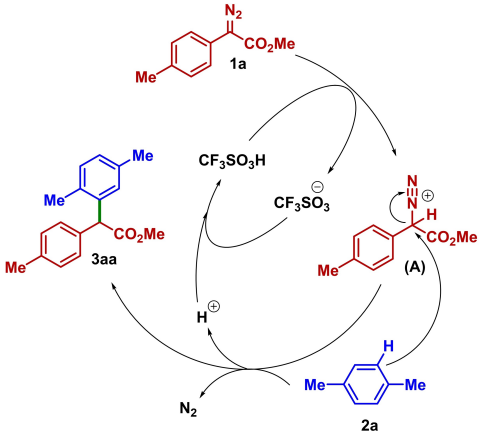
Scheme 2. Gram-Up Reaction and Synthetic Application.

To understand the reaction mechanism, the control experiment was performed (Scheme 3). In this deuterium experiment, TfOH and deuterated benzene (D_6-**2b**) acted as proton sources during the anhydrous solvent reaction as the hydrogen and deuterium were incorporated in the final product D_6-**3ab** (determined by NMR spectroscopy; see the Supporting Information for details).

Based on our previous mechanistic studies,[22] literature precedence,[24] and control experiment, we proposed a plausible reaction mechanism outlined in Scheme 4. The diazonium ion intermediate **A** could be generated from methyl α-(*p*-tolyl)-α-diazoacetate (**1a**) in the presence of TfOH catalyst. Then, the diazonium ion **A**, which would undergo a nucleophilic addition reaction with *p*-xylene (**2a**), provides the desired product diarylacetate **3aa** after the intermolecular C–H functionalization



Scheme 3. Control Experiment.



Scheme 4. Proposed Reaction Mechanism.

extrudes N_2. This mechanism is different compared with Burtoloso's work,[20] in which the quinone type intermediate from methoxy substituted α-aryl-α-diazoesters by H_2SO_4–SiO_2 underwent the Friedel-Crafts alkylation reaction with a phenolic-based nucleophile.

In summary, we have developed an efficient time-economical TfOH-catalyzed C–H activation of α-aryl-α-diazoesters with arenes under mild conditions, offering a way to construct various diarylacetate derivatives. The significant feature of this process is tolerated a range of functional groups with good yields. Further applications of this strategy for the synthesis of biological and pharmaceutical compounds are ongoing in our laboratory.

Experimental Section

General Method: All reactions were carried out in Schlenk tubes. Flash column chromatography was performed over a silica gel. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AM400 spectrometer; chemical shifts (in ppm) were referred to $CDCl_3$ (δ = 7.26 ppm). The ^{13}C NMR spectrum was obtained using the same NMR spectrometer and was calibrated with $CDCl_3$ (δ = 77.0 ppm). The following abbreviations are used to illuminate the diversities: δ = chemical shifts, J = coupling constant, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High-resolution mass spectrometry (HRMS) was performed using a Bruker micrOTOF spectrometer (ESI). All of the solvents were distilled. The heat source is an oil bath. All chemicals were obtained from commercial suppliers unless otherwise stated. PE = petroleum ether and EA = ethyl acetate.

Acknowledgments

This work was supported by Fudan University (JIH1615060).

Conflict of Interest

The authors declare no conflict of interest.

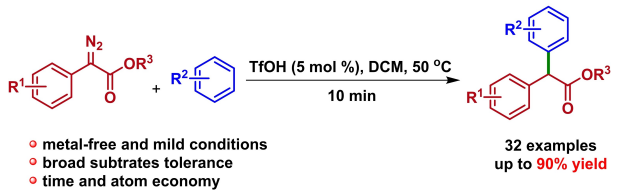
Keywords: TfOH · arylation · α-aryl-α-diazoesters · arenes · diarylacetates

[1] a) M. A. Farajzadeh, A. S. Hojghan, M. R. A. Mogaddam, *J. Food Compos. Anal.* **2018**, *66*, 90–97; b) S. Faruqi, C. Wright, R. Thompson, A. H. Morice, *Br. J. Clin. Pharmacol.* **2014**, *78*, 1272–1280; c) T. Minagawa, M. Gotoh, O. Yokoyama, K. Sugaya, T. Yamanishi, K. Kawahara, K. Kaga, T. Kikuchi, O. Nishizawa, F. s. group, *Int. J. Urol.* **2018**, *25*, 486–491; d) S. Murgas, D. Adolf, *Research and Reports in Urology* **2019**, *11*, 9–13; e) S. Nishijima, K. K. Sugaya, K. Ashitomi, T. Ueda, H. Yamaoto, *Biomedical Research (Tokyo)* **2019**, *40*, 145–152; f) Z. Tavsan, H. A. Kayalı, *Process Biochemistry* **2014**, *49*, 745–750.
[2] G. Spitzmaul, F. Gumilar, J. P. Dilger, C. Bouzat, *Br. J. Pharmacol.* **2009**, *157*, 804–817.
[3] S. Yokoyama, Y. Fujino, Y. Kawamoto, A. Kaneko, T. Fujie, *Chem. Pharm. Bull.* **1994**, *42*, 1351–1353.
[4] a) Y. F. Chen, H. Y. Tsai, K. J. Wu, L. R. Siao, W. G. Wood, *PLoS One* **2013**, *8*, e75654; b) M. M. Lee, Y. Y. Chen, P. Y. Liu, S. Hsu, M. J. Sheu, *Chem.-Biol. Interact.* **2015**, *236*, 19–30; c) M. J. Sheu, P. Y. Chou, C. S. Huang, I. C.

Tsai, Y. C. Chien, S. Y. Lin, H. Y. Tsai, H. C. Cheng, C. H. Wu, *Clin. Exp. Pharmacol. Physiol.* **2010**, *37*, 605–612.
[5] a) M. Camilleri, *Neurogastroenterol Motil* **2008**, *20*, 971–979; b) L. A. Szarka, M. Camilleri, D. Burton, J. C. Fox, S. McKinzie, T. Stanislav, J. Simonson, N. Sullivan, A. R. Zinsmeister, *Clin. Gastroenterol. Hepatol.* **2007**, *5*, 1268–1275.
[6] a) G. B. Leslie, G. E. Conway, *Pharmacol. Res. Commun.* **1970**, *2*, 201–204; b) M. G. Palfreyman, E. S. C. Palfreyman, M. S. G., *Eur. J. Pharmacol.* **1974**, *28*, 379–383.
[7] a) W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002; b) B. Song, T. Himmler, L. J. Gooßen, *Adv. Synth. Catal.* **2011**, *353*, 1688–1694.
[8] a) Y. Kim, Y. S. Choi, S. K. Hong, Y. S. Park, *Org. Biomol. Chem.* **2019**, *17*, 4554–4563; b) P.-S. Lai, J. A. Dubland, M. G. Sarwar, M. G. Chudzinski, M. S. Taylor, *Tetrahedron* **2011**, *67*, 7586–7592.
[9] Q. Xu, B. Li, Y. Ma, F. Sun, Y. Gao, N. Ye, *Org. Biomol. Chem.* **2020**, *18*, 666–670.
[10] R. B. Kothapalli, R. Niddana, R. Balamurugan, *Org. Lett.* **2014**, *16*, 1278–1281.
[11] a) Y. Zhang, J. Wang, *Chem. Commun.* **2009**, 5350–5361; b) J. N. Johnston, H. Muchalski, T. L. Troyer, *Angew. Chem. Int. Ed.* **2010**, *49*, 2290–2298; *Angew. Chem.* **2010**, *122*, 2340–2349; c) S. F. Zhu, Q. L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365–1377; d) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427–2440; e) H. Keipour, V. Carreras, T. Ollevier, *Org. Biomol. Chem.* **2017**, *15*, 5441–5456; f) L. W. Ciszewski, K. Rybicka-Jasinska, D. Gryko, *Org. Biomol. Chem.* **2019**, *17*, 432–448.
[12] a) J. M. Yang, Y. Cai, S. F. Zhu, Q. L. Zhou, *Org. Biomol. Chem.* **2016**, *14*, 5516–5519; b) B. Wang, I. G. Howard, J. W. Pope, E. D. Conte, Y. Deng, *Chem. Sci.* **2019**, *10*, 7958–7963.
[13] a) J. Ghorai, P. Anbarasan, *J. Org. Chem.* **2015**, *80*, 3455–3461; b) Y. Xia, Z. Liu, S. Feng, F. Ye, Y. Zhang, J. Wang, *Org. Lett.* **2015**, *17*, 956–959; c) B. Xu, M. L. Li, X. D. Zuo, S. F. Zhu, Q. L. Zhou, *J. Am. Chem. Soc.* **2015**, *137*, 8700–8703.
[14] C. P. Owens, A. Varela-Álvarez, V. Boyarskikh, D. G. Musaev, H. M. L. Davies, S. B. Blakey, *Chem. Sci.* **2013**, *4*, 2590–2596.
[15] S. M. Golitsin, I. P. Beletskaya, I. D. Titanyuk, *Synthesis* **2020**, *52*, 775–780.
[16] a) E. Tayama, T. Yanaki, H. Iwamoto, E. Hasegawa, *Eur. J. Org. Chem.* **2010**, *2010*, 6719–6721; b) E. Tayama, M. Ishikawa, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett.* **2012**, *53*, 5159–5161.
[17] a) Y. Xi, Y. Su, Z. Yu, B. Dong, E. J. McClain, Y. Lan, X. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 9817–9821; *Angew. Chem.* **2014**, *126*, 9975–9979; b) Z. Yu, B. Ma, M. Chen, H. H. Wu, L. Liu, J. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 6904–6907; c) B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu, J. Zhang, *Angew. Chem. Int. Ed.* **2017**, *56*, 2749–2753; *Angew. Chem.* **2017**, *129*, 2793–2797; d) B. Ma, J. Wu, L. Liu, J. Zhang, *Chem. Commun.* **2017**, *53*, 10164–10167; e) W. Zhang, G. Xu, L. Qiu, J. Sun, *Org. Biomol. Chem.* **2018**, *16*, 3889–3892; f) L. Carreras, A. Franconetti, A. Grabulosa, A. Frontera, A. Vidal-Ferran, *Org. Chem. Front.* **2020**, *7*, 1626–1634.
[18] a) A. F. da Silva, M. A. S. Afonso, R. A. Cormanich, I. D. Jurberg, *Chem. Eur. J.* **2020**, *26*, 5648–5653; b) C. Peng, W. Zhang, G. Yan, J. Wang, *Org. Lett.* **2009**, *11*, 1667–1670.
[19] Z. Yu, Y. Li, J. Shi, B. Ma, L. Liu, J. Zhang, *Angew. Chem. Int. Ed.* **2016**, *55*, 14807–14811; *Angew. Chem.* **2016**, *128*, 15027–15031.
[20] R. D. C. Gallo, P. B. Momo, D. P. Day, A. C. B. Burtoloso, *Org. Lett.* **2020**, *22*, 2339–2343.
[21] S. Hu, J. Wu, Z. Lu, J. Wang, Y. Tao, M. Jiang, F. Chen, *J. Org. Chem.* **2020**. DOI: 10.1021/acs.joc.0c02588.
[22] S. Hu, Z. Lu, M. Liu, H. Xu, J. Wu, F. Chen, *J. Org. Chem.* **2020**, *85*, 14916–14925.
[23] M. He, Y. Chen, Y. Luo, J. Li, R. Lai, Z. Yang, Y. Wang, Y. Wu, *Green Synth. Catal.* **2020**, *1*, 180–182.
[24] C. Zhai, D. Xing, C. Jing, J. Zhou, C. Wang, D. Wang, W. Hu, *Org. Lett.* **2014**, *16*, 2934–2937.

Manuscript received: February 19, 2021
Revised manuscript received: March 8, 2021
Accepted manuscript online: March 18, 2021
Version of record online: ■■, ■■■

COMMUNICATIONS



Tick-tock: A time-economical synthesis of diarylacetates by TfOH-catalyzed arylation of α-aryl-α-diazoesters with arenes is described. This protocol provides a variety of diarylacetates in good yields with broad substrate scope, excellent functional group compatibility, and mild reaction conditions.