Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 34–36

Mendeleev Communications

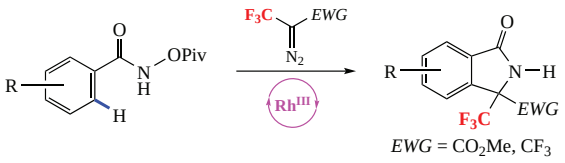
Synthesis of CF_3-substituted isoindolones *via* rhodium(III)-catalyzed carbenoid C–H functionalization of aryl hydroxamates

Daria V. Vorobyeva, Alexandra S. Bubnova, Anastasiya G. Buyanovskaya and Sergey N. Osipov*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: osipov@ineos.ac.ru

DOI: 10.1016/j.mencom.2023.01.010

An efficient method for the selective preparation of trifluoromethyl-substituted isoindolones has been developed *via* Rh^{III}-catalyzed C–H activation/[4 + 1]-annulation of aryl hydroxamates with functionalized acceptor/acceptor diazo compounds as cross-coupling partners.



Keywords: aryl hydroxamates, C–H activation, diazo compounds, rhodium(III) catalysis, isoindolones, organofluorine compounds.

Isoindolone derivatives constitute important structural units found in numerous bioactive molecules, pharmaceuticals and natural products with interesting therapeutic activities.[1] Among them, isoindolone-3-carboxylates and their derivatives are of particular interest. Besides exhibiting a wide spectrum of biological properties[2] such as antidiabetic, antihypertensive, and antiarrhythmic and antiviral activities they serve as universal building blocks for enantioselective Michael reaction,[3] spirolactonization,[4] hydrogenated octahydroisoindole core structure,[5] and large scale syntheses of pharmaceuticals.[2(a)] Therefore, development of efficient catalytic methods for the convenient synthesis of these scaffolds is highly appealing.

The transition metal-catalyzed C–H functionalization of (hetero)arenes with various coupling partners assisted by directing groups is one of the prominent strategies to construct variety of valuable heterocycles.[6] Among them, diazo compounds have been widely utilized in carbenoid C–H activation *via* carbene migratory insertion pathways under Rh, Ir, or Co catalysis to access different types of alkylation or annulation products (Figure 1).[7] In 2013, Rovis reported a Rh^{III}-catalyzed C–H activation of *N*-alkoxybenzamides with donor/acceptor diazo compounds[8] to afford isoindolones bearing a quaternary carbon center. The asymmetric version of this type of transformations has been developed by Cramer one year later.[9] Same year Yu *et al*. reported a similar reaction of *N*-alkoxybenzamides with α-diazo esters.[10] In this study, the rhodacyclic intermediate was isolated and characterized by X-ray crystallography, which provided direct proof that C–H/N–H cyclometalation was a key step in the catalytic cycle. Diazo compounds of donor/acceptor type were used in most cases described. The annulation reactions of acceptor/acceptor diazo compounds to access isoindolone derivatives have been explored just on a few examples of diazomalonates towards *O*-(acetyl)benzenehydroxamic acids under rather big loading of rhodium catalyst $[Cp^*RhCl_2]_2$.[10]

Given the great importance of fluorine-containing compounds in modern drug discovery process,[†,11] we have recently achieved the *ortho*-selective (hetero)arene C–H coupling with 3,3,3-trifluoro-2-diazopropionate being a unique synthon for simultaneous installation of two pharmacophore groups (CF_3 and CO_2R) into organic molecules.[12] Thus, aryl ketone methoximes, *N*-arylpyrazoles,[13] 6-arylpurines[14,15] and *N*-pyrimidylindole[16] have proved to be effective substrates for that catalytic transformation (Figure 1). Herein we report a direct Rh^{III}-catalyzed C–H activation/[4 + 1]-annulation of aryl hydroxamates using fluorinated acceptor/acceptor diazo compounds as the cross-coupling partners to afford new

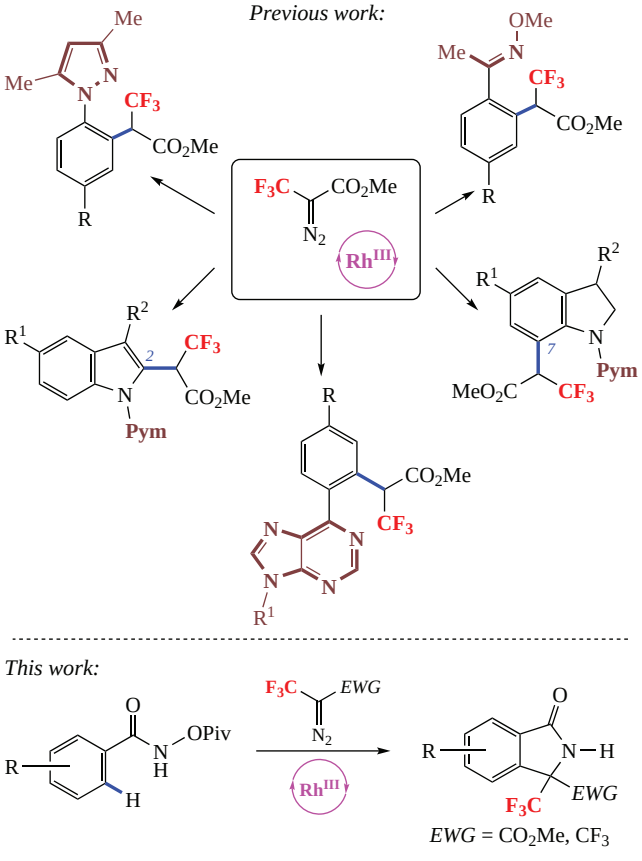
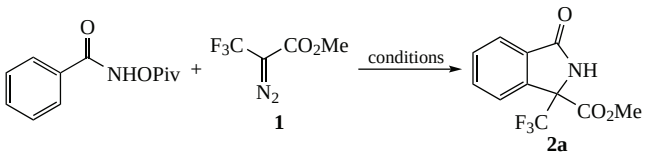


Figure 1 CF_3-Carbenoid functionalization of (hetero)arenes.

† In 2020, approximately 25% (14 of 53) of all drugs approved by the FDA contained fluorine. For a recent review, see ref. 11.



1 **2a**

Scheme 1

Table 1 Optimization of the C–H activation / annulation reaction.[a]

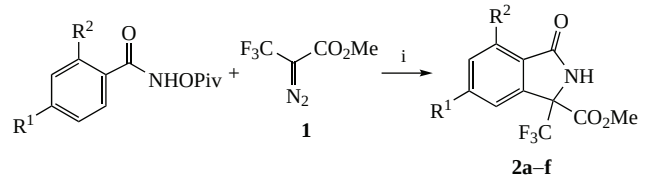
Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Yield[b] of **2a** (%)
1	$[Cp^*RhCl_2]_2$ (2.5)	$AgSbF_6$ (10)	$ClCH_2CH_2Cl$	0
2	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc (30)	$ClCH_2CH_2Cl$	76 (58)
3	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc (30)	MeOH	85
4	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc (30)	THF	96
5	$[Cp^*RhCl_2]_2$ (2.5)	CsOAc (30)	MeCN	100
6	$[Cp^*RhCl_2]_2$ (2.5)	NaOAc (30)	MeCN	100
7	**$[Cp^*RhCl_2]_2$ (2.0)**	**CsOAc (10)**	**MeCN**	**100 (92)**
8	$[Cp^*RhCl_2]_2$ (1.5)	CsOAc (10)	MeCN	75
9	$[Cp^*RhCl_2]_2$ (2.5)	–	MeCN	70
10	–	CsOAc (30)	MeCN	0
11	$[Cp^*IrCl_2]_2$ (5.0)	CsOAc (30)	MeCN[c]	0
12	$[Cp^*CoI_2]_2$ (5.0)	CsOAc (30)	MeCN[c]	0

[a] *Reagents and conditions*: *N*-(pivaloyloxy)benzamide (0.2 mmol), diazo compound **1** (0.22 mmol), solvent (3 ml), argon, 40 °C. [b] From ^{19}F NMR, isolated yields are given in parentheses. [c] The reaction was performed at 100 °C.

isoindolone derivatives. To the best of our knowledge, synthesis of trifluoromethyl-substituted isoindolone-3-carboxylates as well as 3,3-bis(trifluoromethyl)isoindolones have not been realized up to date.

We commenced our study with the reaction between *N*-(pivaloyloxy)benzamide and readily available methyl 3,3,3-trifluoro-2-diazopropionate **1** for the screening of optimal conditions for the annulation (Scheme 1). First, the attempted experiment under conditions previously found for CF_3-carbene C–H functionalization of *N*-arylpyrazoles and aryl ketone methoximes ($[Cp^*RhCl_2]_2/AgSbF_6$ in 1,2-dichloroethane)[13] failed (Table 1, entry 1). Fortunately, the replacing of silver additive with cesium acetate resulted in smooth reaction to give isoindolone **2a** in 76% NMR yield (entry 2). Acetonitrile was identified as the most effective solvent (entries 2–5). The reaction should be best performed in the presence of 2.0 mol% $[Cp^*RhCl_2]_2$ and 10 mol% CsOAc in MeCN under argon at 40 °C for 3 h to afford the desired [4 + 1]-cycloaddition product **2a** in high yield (entry 7). The reaction could also proceed in the absence of any additives, however, the full conversion was never achieved even under prolonged reaction time (entry 9). Iridium- and cobalt-based catalytic systems proved to be ineffective (entries 11, 12).

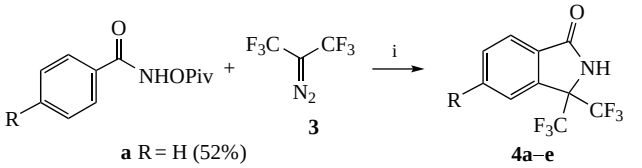
With the optimized conditions in hand, we examined a series of substituted aryl hydroxamates (Scheme 2) and prepared



1 **2a–f**

a $R^1 = R^2 = H$ (91%)
b R^1 = Me, R^2 = H (84%)
c R^1 = OMe, R^2 = H (93%)
d $R^1 = CF_3$, R^2 = H (74%)
e $R^1 = NO_2$, R^2 = H (60%)
f R^1 = H, R^2 = Me (0%)

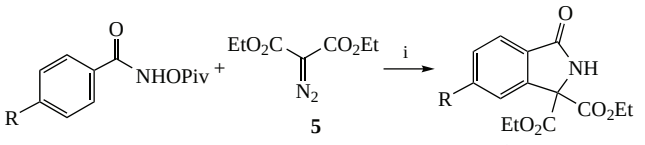
Scheme 2 *Reagents and conditions*: i, $[Cp^*RhCl_2]_2$ (2 mol%), CsOAc (10 mol%), MeCN, argon, 40–70 °C, 3 h.



3 **4a–e**

a R = H (52%)
b R = Me (50%)
c R = OMe (40%)
d R = CF_3 (66%)
e R = NO_2 (60%)

Scheme 3 *Reagents and conditions*: i, $[Cp^*RhCl_2]_2$ (2 mol%), CsOAc (10 mol%), MeCN, 70 °C, 3 h.



5 **6a–e**

a R = H (75%)
b R = Me (63%)
c R = OMe (74%)
d R = CF_3 (88%)
e R = NO_2 (60%)

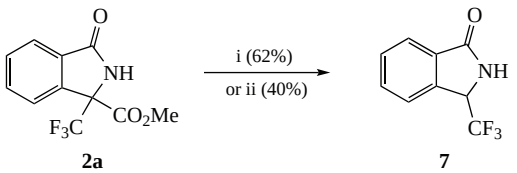
Scheme 4 *Reagents and conditions*: i, $[Cp^*RhCl_2]_2$ (2 mol%), CsOAc (10 mol%), MeCN or THF, argon, 70 °C.

the corresponding 3-methoxycarbonyl-3-(trifluoromethyl)isoindolones **2a–e** in good to excellent yields. The electronic nature of substituents in aromatic ring does not significantly affect the outcome of the reaction. However, the reaction with aryl hydroxamates bearing electron-withdrawing groups (CF_3 and NO_2) required heating up to 70 °C to reach full conversion. It is noteworthy, that in the case of an *ortho*-substituted phenyl ring all our attempts to induce conversion of the starting hydroxamate and to obtain product **2f** have proved to be unsuccessful.

Next, we investigated the reactivity of 1,1,1,3,3,3-hexafluoro-2-diazopropane **3**[17] which had not previously been applied in any metal-catalyzed C–H functionalization of (hetero)arenes (Scheme 3). Its reactions with aryl hydroxamates occur readily at 70 ºC in acetonitrile when using the same catalytic system as for **1** and afforded the corresponding 3,3-bis(trifluoromethyl)-isoindolones **4a–e** in moderate to good yields (Scheme 3).

We were also interested in studying the behavior of one more acceptor/acceptor diazo compound, namely, diethyl diazomalonate **5**. There is just one documented[10] example of its application in similar reaction with *N*-acetoxybenzamide under catalysis with 5 mol% of $[Cp^*RhCl_2]_2$. We found herein that the reaction proceeded smoothly at 70 ºC in MeCN in the presence of 2.0 mol% of $[Cp^*RhCl_2]_2$ and 10 mol% of CsOAc to afford the desired products **6a–e** in good yields (Scheme 4). Slightly higher yields were indicated for products **6d**,**e** when the reaction was run in THF.

Finally, we demonstrated one of the possible synthetic applications of the synthesized isoindolones **2**. The saponification of compound **2a** with KOH in methanol leads to decarboxylation product **7** in 62 % yield (Scheme 5). The same compound can be also obtained under acid hydrolysis conditions in lower yield of 40 %. An alternative pathway to **7** and its derivatives *via* Pd-catalyzed intramolecular aminocarbonylation of 2,2,2-trifluoro-



2a **7**

Scheme 5 *Reagents and conditions*: i, KOH (5%), MeOH–H_2O, room temperature, 2 h; ii, HCl (6 N), MeCN.

1-(2-iodophenyl)ethan-1-amine has been previously reported by Fustero *et al*.[18]

In summary, we have elaborated an efficient procedure for the preparation of trifluoromethyl-substituted isoindolones based on Rh^{III}-catalyzed C–H activation/[4 + 1]-annulation of aryl hydroxamates with functionalized acceptor/acceptor diazo compounds as the cross-coupling partners. The reactions proceed smoothly with high regioselectivity within 3–4 h in acetonitrile in the presence of 2 mol% $[Cp^*RhCl_2]_2$ and 10 mol% of cesium acetate as additive and allowed the simultaneous introduction of two pharmacophoric CF_3 and carboxylate functions into position 3 of isoindolone core.

This work was financially supported by the Russian Science Foundation (grant no. 21-13-00328). NMR studies, spectral characterization and elemental analyses were performed with the support from the Ministry of Science and Higher Education of the Russian Federation using the equipment of the Center for Molecular Composition Studies of INEOS RAS section.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.010.

References

1 (*a*) A. C. Bishop, J. A. Ubersax, D. T. Petsch, D. P. Matheos, N. S. Gray, J. Blethrow, E. Shimizu, J. Z. Tsien, P. G. Schultz, M. D. Rose, J. L. Wood, O. David, D. O. Morgan and K. M. Shokat, *Nature*, 2000, **407**, 395; (*b*) E. C. Lawson, D. K. Luci, S. Ghosh, W. A. Kinney, C. H. Reynolds, J. Qi, C. E. Smith, Y. Wang, L. K. Minor, B. J. Haertlein, T. J. Parry, B. P. Damiano and B. E. Maryanoff, *J. Med. Chem*., 2009, **52**, 7432.

2 (*a*) S. A. Eisenbeis, R. Chen, M. Kang, M. Barrila and R. Buzon, *Org. Process Res. Dev*., 2015, **19**, 244; (*b*) S. Trivedi, K. Dekermendjian, R. Julien, J. Huang, P.-E. Lund, J. Krupp, R. Kronqvist, O. Larsson and R. Bostwick, *Assay Drug Dev. Technol*., 2008, **6**, 167; (*c*) I. Macsari, Y. Besidski, G. Csjernyik, L. I. Nilsson, L. Sandberg, U. Yngve, K. Åhlin, T. Bueters, A. B. Eriksson, P.-E. Lund, E. Venyike, S. Oerther, K. H. Blakeman, L. Luo and P. Arvidsson, *J. Med. Chem*., 2012, **55**, 6866; (*d*) J. Wrobel, A. Dietrich, S. A. Woolson, J. Millen, M. McCaleb, M. C. Harrison, T. C. Hohman, J. Sredy and S. Sullivan, *J. Med. Chem*., 1992, **35**, 4613; (*e*) M. Anzini, A. Capelli, S. Vomero, G. Giorgi, T. Langer, G. Bruni, M. R. Romero and A. S. Basile, *J. Med. Chem*., 1996, **39**, 4275; (*f*) A. Mertens, J. H. Zilch, B. Konig, W. Schafer, T. Poll, W. Kampe, S. Seidel, U. Leser and H. Leinert, *J. Med. Chem*., 1993, **36**, 2526.

3 (*a*) F. Scorzelli, A. Di Mola, L. Palombi and A. Massa, *Molecules*, 2015, **20**, 8484; (*b*) F. Scorzelli, A. Di Mola, L. Palombi, R. Filosa and A. Massa, *Synth. Commun*., 2015, **45**, 1552; (*c*) F. Scorzelli, A. Di Mola, F. De Piano, C. Tedesco, L. Palombi, R. Filosa, M. Waser and A. Massa, *Tetrahedron*, 2017, **73**, 819; (*d*) A. Massa, P. Rizzo, F. Scorzelli, G. Monaco and R. Zanasi, *J. Pharm. Biomed. Anal*., 2017, **144**, 52.

4 (*a*) M. M. Rammah, M. Othman, K. Ciamala, C. Strohmann and M. B. Rammah, *Tetrahedron*, 2008, **64**, 3505; (*b*) A. Pesquet and M. Othman, *Tetrahedron Lett*., 2013, **54**, 5227.

5 S. Nieto, F. J. Sayago, P. Laborda, T. Soler, C. Cativiela and E. P. Urriolabeitia, *Tetrahedron*, 2011, **67**, 4185.

6 (*a*) A. Ros, R. Fernández and J. M. Lassaletta, *Chem. Soc. Rev*., 2014, **43**, 3229; (*b*) M.-L. Louillat and F. W. Patureau, *Chem. Soc. Rev*., 2014, **43**, 901; (*c*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front*., 2015, **2**, 1107; (*d*) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev*., 2017, **117**, 9163; (*e*) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247; (*f*) W. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front*., 2017, **4**, 1435; (*g*) R. Manikandan and M. Jeganmohan, *Chem. Commun*., 2017, **53**, 8931; (*h*) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev*., 2017, **117**, 9333; (*i*) J. C. K. Chu and T. Rovis, *Angew. Chem., Int. Ed*., 2018, **57**, 62; (*j*) T. Gensch, M. J. James, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed*., 2018, **57**, 2296; (*k*) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603; (*l*) L.-R. Song, Z. Fan and A. Zhang, *Org. Biomol. Chem.*, 2019, **17**, 1351; (*m*) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi and J.-A. Ma, *Chem. Soc. Rev*., 2019, **48**, 4921; (*n*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev*., 2019, **119**, 2192.

7 (*a*) Y. Xia, D. Qiu and J. Wang, *Chem. Rev*., 2017, **117**, 13810; (*b*) F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun*., 2015, **51**, 7986.

8 T. K. Hyster, K. E. Ruhl and T. Rovis, *J. Am. Chem. Soc*., 2013, **135**, 5364.

9 B. Ye and N. Cramer, *Angew. Chem., Int. Ed*., 2014, **53**, 7896.

10 H.-W. Lam, K.-Y. Man, W.-W. Chan, Z. Zhou and W.-Y. Yu, *Org. Biomol. Chem*., 2014, **12**, 4112.

11 B. G. de la Torre and F. Albericio, *Molecules*, 2021, **26**, 627.

12 (*a*) S. N. Osipov, N. Sewald, K. Burger, A. F. Kolomiets and A. V. Fokin, *Tetrahedron Lett*., 1996, **37**, 615; (*b*) D. V. Vorobyeva, A. K. Mailyan, A. S. Peregudov, N. M. Karimova, T. P. Vasilyeva, I. S. Bushmarinov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Tetrahedron*, 2011, **67**, 3524; (*c*) D. V. Vorobyeva, I. D. Titanyuk, I. P. Beletskaya and S. N. Osipov, *Mendeleev Commun*., 2005, 222; (*d*) A. K. Mailyan, I. M. Krylov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Synlett*, 2011, 2321; (*e*) A. K. Mailyan, A. S. Peregudov, P. H. Dixneuf, C. Bruneau and S. N. Osipov, *J. Org. Chem*., 2012, **77**, 8518; (*f*) A. K. Mailyan, I. M. Krylov, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Eur. J. Org. Chem*., 2013, 5353; (*g*) I. E. Tsyshchuk, D. V. Vorobyeva, A. S. Peregudov and S. N. Osipov, *Eur. J. Org. Chem*., 2014, 2480.

13 I. E. Tsyshchuk, D. V. Vorobyeva, A. S. Peregudov and S. N. Osipov, *Eur. J. Org. Chem*., 2015, 4950.

14 I. E. Iagafarova, D. V. Vorobyeva, D. A. Loginov, A. S. Peregudov and S. N. Osipov, *Eur. J. Org. Chem*., 2017, 840.

15 M. M. Vinogradov, D. V. Vorobyeva, Yu. V. Nelyubina, S. N. Osipov and D. A. Loginov, *Mendeleev Commun*., 2020, **30**, 494.

16 D. V. Vorobyeva, M. M. Vinogradov, Yu. V. Nelyubina, D. A. Loginov, A. S. Peregudov and S. N. Osipov, *Org. Biomol. Chem*., 2018, **16**, 2966.

17 V. V. Linev, A. F. Kolomiets and A. V. Fokin, *Bull. Russ. Acad. Sci., Div. Chem. Sci*., 1992, **41**, 360 (*Izv. Akad. Nauk, Ser. Khim*., 1992, 452).

18 P. Barrio, I. Ibáñez, L. Herrera, R. Román, S. Catalán, and S. Fustero, *Chem. – Eur. J*., 2015, **21**, 1157.

Received: 11th July 2022; Com. 22/6952