How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 18478–18483
International Edition: doi.org/10.1002/anie.202103323
German Edition: doi.org/10.1002/ange.202103323

Synthetic Methods

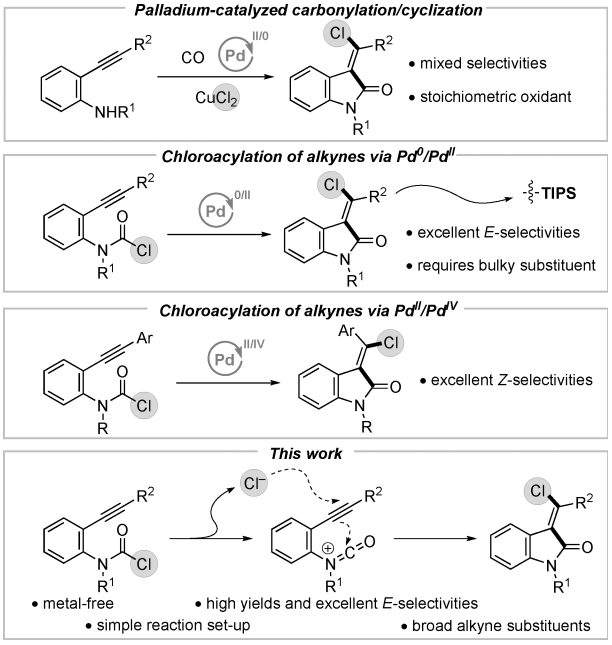
Cycloisomerization of Carbamoyl Chlorides in Hexafluoroisopropanol: Stereoselective Synthesis of Chlorinated Methylene Oxindoles and Quinolinones

*José F. Rodríguez, Anji Zhang, Jonathan Bajohr, Andrew Whyte, Bijan Mirabi, and Mark Lautens**

Abstract: *Hexafluoroisopropanol (HFIP) was employed as an additive for the generation of 3-(chloromethylene)oxindoles via the chloroacylation of alkyne-tethered carbamoyl chlorides. This reaction avoids the use of a metal catalyst and accesses products in high yields and stereoselectivities. Additionally, this reaction is scalable and proved amenable to a series of product derivatizations, including the synthesis of nintedanib. The reactivity of alkene-tethered carbamoyl chlorides with hexafluoroisopropanol (HFIP) was harnessed towards the synthesis of 2-quinolinones.*

Methylene oxindoles display a broad range of biological activities and have become key targets in medicinal chemistry.[1] As a result, several strategies have been developed for their preparation.[2,3] Further solidifying the importance of these compounds is their synthetic versatility, which has been exploited in the total synthesis of spirocyclic oxindole natural products;[4,5] scaffolds such as 3-(halomethylene)oxindoles are useful intermediates for accessing these medicinally active motifs.[6] Nevertheless, highly stereoselective methods for their preparation are scarce in the literature and commonly require precious transition-metal-based catalysts. Consequently, the development of metal-free methodologies for the stereoselective synthesis of 3-(halomethylene)oxindoles is of considerable interest.

In 2007, a Pd^{II}-catalyzed carbonylative annulation of 2-alkynylanilines was reported by Li and co-workers (Scheme 1).[7] This report employs $CuCl_2$ as a stoichiometric oxidant and generates (*E*)-3-(chloromethylene)oxindoles in moderate yields, displaying stereoselectivities ranging from 2.7:1 to > 99:1. In 2015, our group reported a complementary synthesis of these scaffolds via a Pd^0-catalyzed chloroacylation of alkyne-tethered carbamoyl chlorides;[8a] however, sterically bulky alkynyl substituents were required to promote a challenging C(sp^2)–Cl reductive elimination.[8–10] Addressing this limitation, our group reported a Pd^{II}-catalyzed synthesis of the corresponding *Z*-isomers in good yields and excellent stereoselectivities.[11]



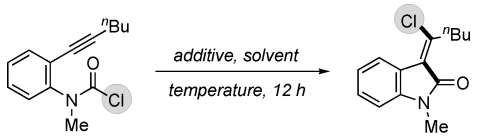
Scheme 1. Strategies for the synthesis of 3-(chloromethylene)oxindoles.

While cycloisomerizations from readily available organohalides are a powerful method to introduce molecular complexity and retain the halide functionality, these reactions typically require transition-metal catalysts which can impose substrate limitations.[8–10] When searching for new methodologies for the synthesis of (*E*)-3-(chloromethylene)oxindoles, we found that fluorinated alcohol additives promote the intramolecular carbochlorination of alkynes without metal catalysts. We describe herein a metal-free, simple, and effective cycloisomerization of alkyne-tethered carbamoyl chlorides for the synthesis of these scaffolds.

We envisioned using alkyne-tethered carbamoyl chloride **1a** as a substrate for an alkyne chloroacylation process similar to previous reports from our group.[8a,11a] We discovered the propensity of alkyne-tethered carbamoyl chlorides to cycloisomerize in the presence of TFE at high temperatures. Product **2a** was generated in 52% yield and high *E*-selectivity by heating **1a** in TFE (Table 1, entry 1). Notably, the olefin stereochemistry was complementary to our previous Pd^{II}-catalyzed chloroacylation report.[11] Alcoholic solvents lacking fluorine atoms were ineffective in this reaction, which is

[*] J. F. Rodríguez, A. Zhang, J. Bajohr, A. Whyte, B. Mirabi, Prof. Dr. M. Lautens
Davenport Research Laboratories, Department of Chemistry, University of Toronto
80 St. George Street, Toronto, Ontario M5S 3H6 (Canada)
E-mail: mark.lautens@utoronto.ca
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202103323.

Table 1: Synthesis of methylene oxindoles: Optimization of reaction conditions. Reactions were performed on a 0.2 mmol scale. NMR yields and isomeric ratios determined using CH_2Br_2 as internal standard. Isolated yield given in parenthesis.



1a (0.2 mmol) **2a**

Entry	Solvent (0.2 M)	Temp. (°C)	Additive	Yield **2a** (%)	*E*/*Z* ratio
1	TFE	100	None	52	20:1
2	HFIP	100	None	71	>20:1
3	HFIP	80	None	27	2.2:1
4	**PhMe**	**100**	**HFIP (8 equiv)**	**96 (94)**	**>20:1**
5	PhMe	100	HFIP (3 equiv)	34	>20:1
6	PhMe	100	^{i}PrOH (8 equiv)	11	N. D.
7	PhMe	100	None	N. D.	N. D.
8	MeCN	100	None	10	>20:1
9[a]	NMP	150	None	N. D.	N. D.
10	PhMe	100	TFA (8 equiv)	61	>20:1
11	PhMe	100	AcOH (8 equiv)	N. D.	N. D.
12	PhMe	100	BzOH (8 equiv)	N. D.	N. D.
13[a]	PhMe	100	TfOH (8 equiv)	N. D.	N. D.

N. D. = Not detected. [a] Complete decomposition of starting material.

attributed to the distinct physical properties of their fluorinated counterparts. These include increased acidity and hydrogen bond-donating ability, reduced nucleophilicity, and the ability to stabilize cationic species.[12] With this observation, an improved yield of 71% and >20:1 *E*/*Z* selectivity was observed when HFIP was employed as the solvent (entry 2).

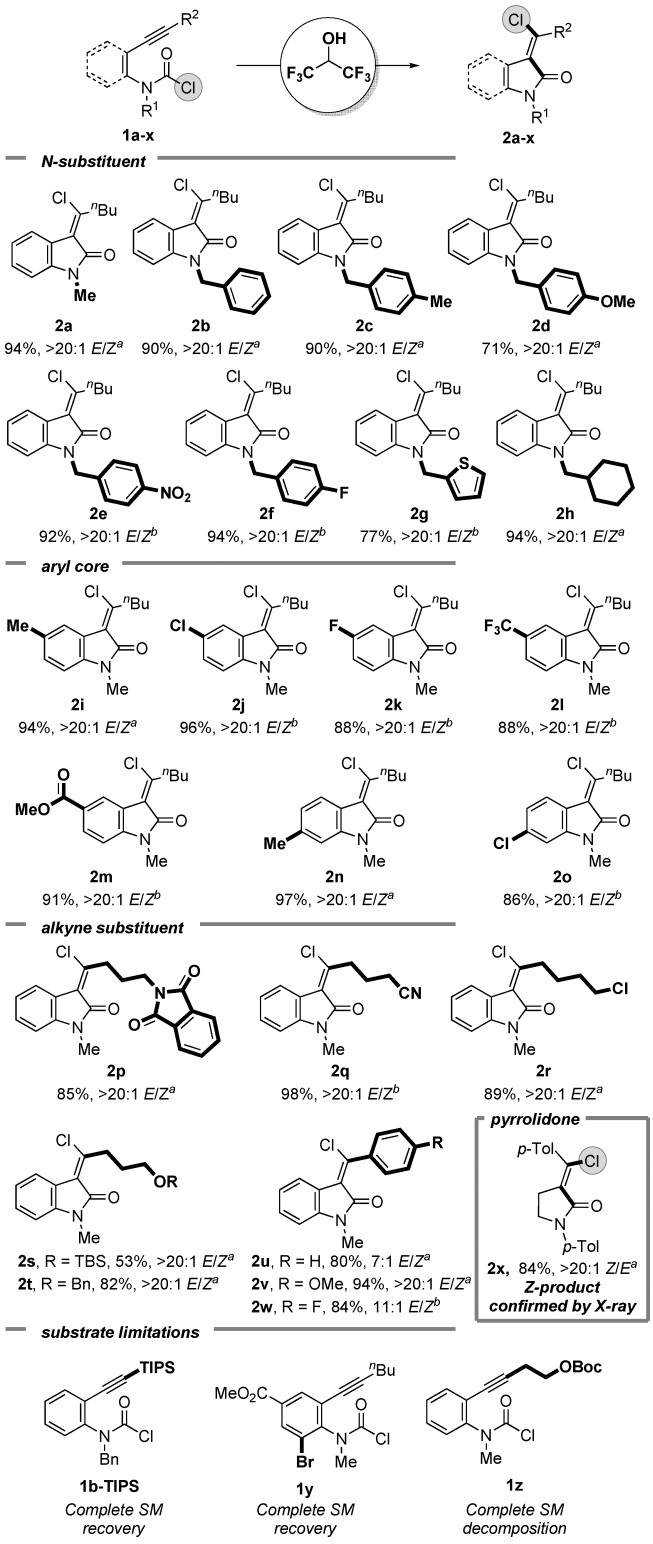
Decreased yield and stereoselectivity was obtained at a lower temperature (entry 3). The loss in stereoselectivity suggests that higher temperatures lead to preferential formation of the more stable isomer (vide infra). Ultimately, 8 equivalents of HFIP in toluene solvent gave the product in 96% yield and >20:1 *E*/*Z* (entry 4). The product was formed in lower yield when 3 equivalents of HFIP were used (entry 5). Interestingly, we observed product formation in 11% yield using a PhMe/^{i}PrOH solvent system (entry 6). Complete recovery of starting material was observed in the absence of HFIP (entry 7). The product was formed in low yields by heating **1a** in acetonitrile (entry 8), while heating the substrate in NMP at 150 °C resulted in decomposition of the starting material (entry 9). TFA was an effective reagent, generating the product in 61% yield and >20:1 *E*/*Z* (entry 10). However, other protic acids were inefficient in this process (entries 11–13).

The generality of this process was evaluated (Scheme 2). Apart from products **2u** and **2w**, which displayed decreased *E*/*Z* ratios, all products were furnished with complete *E*-selectivity. Initially, we examined the effect of substitutions at the nitrogen atom (entries **2a**–**2h**). The corresponding products were obtained in good to excellent yields. The acidic nature of HFIP is responsible for the decreased yields in **2d**, resulting from PMB-group cleavage. Increased HFIP loadings and longer reaction times were required for complete conversion in the presence of electron-withdrawing functionalities (**2e** and **2f**). The effect of various substituents on the aniline core was also investigated (**2i**–**2o**), and the corresponding products were obtained in yields ranging from 86% to 97% yield.

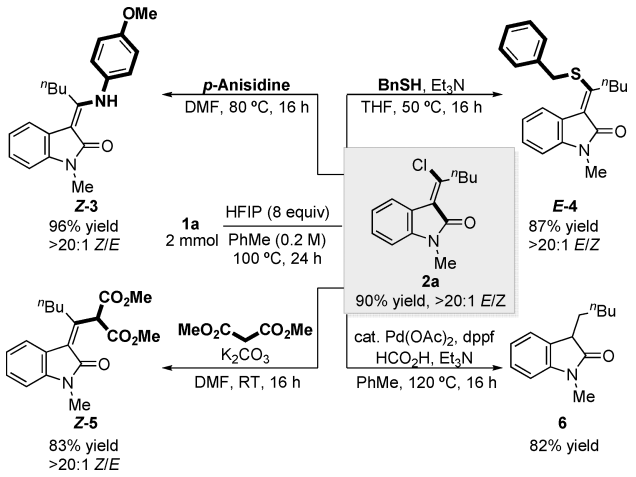
Products containing a variety of alkyne substitutions were synthesized (**2p**–**2w**). The acidity of HFIP may also be responsible for O-TBS cleavage in product **2s**, resulting in diminished yields. Complementary to known methods for the synthesis of (*E*)-3-(chloromethylene)oxindoles,[6c,7] products containing aryl substituents at the alkene were obtained in excellent yields and good selectivities. Product **2u**, encompassing an unsubstituted phenyl group, was formed in 80% yield, and 7:1 *E*/*Z* ratio. Excellent yield and stereoselectivity was obtained when **1v** was employed, containing an electron-rich -OMe substituent. Product **2w**, containing a *p*-fluoride on the aryl moiety, was formed in 84% yield and 11:1 *E*/*Z*. X-ray crystallographic analysis of **2w**[26] served to confirm the *E*-stereochemistry of the products, while ^{1}H NMR analysis was applied for all other examples using characteristic chemical shifts. Chlorinated methylene pyrrolidone **2x** was isolated in 84% yield. In contrast to the oxindole products, the 2-pyrrolidone scaffold was obtained with complete *Z*-selectivity as determined by X-ray crystallographic analysis.[26] The synthesis of this class of compounds has not been achieved by previous metal-catalyzed alkyne chloroacylation reports.[6c,7,8,11a]

We sought to determine the substrate limitations of this reaction. Unreacted starting material was observed when substrate **1b-TIPS** was subjected to the reaction conditions. The bulky TIPS substituent likely hinders addition of the chloride to the alkyne moiety. Similarly, no reaction took place with substrate **1y**, containing a bromide substituent *ortho* to the carbamoyl functionality which may impact its conformation. In addition, substrate **1z**, containing an acid-sensitive alkyl carbonate on the alkyne, led to complete decomposition of the starting material.

The chloroacylation of **1a** was successfully performed on a 2 mmol scale, forming product **2a** in 90% yield and complete *E*-selectivity (Scheme 3). The synthetic utility of the chlorinated methylene oxindole products was determined by carrying out various transformations. Nucleophilic substitution with *p*-anisidine resulted in generation of ***Z*-3** in 96% yield and complete *Z*-selectivity. When benzyl mercaptan was used as a nucleophile, product ***E*-4** was furnished in 87% yield.[11a] Employing dimethyl malonate as the nucleophile generated product ***Z*-5** in 83% yield and >20:1 *Z*/*E* ratio. The stereoselective formation of products ***Z*-3**, ***E*-4**, and ***Z*-5** is likely resulting from a stereoselective addition/elimination mechanism to form the more stable isomer. This phenomenon has been reported by Meyer and Cossy, who observed a shift



Scheme 2. Scope for the HFIP-assisted chloroacylation of alkynes. Reactions run on a 0.2 mmol scale. Values represent isolated yields of **2**. Isomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [a] Reaction performed using 8 equivalents of HFIP, PhMe (0.2 M), and heated at 100 °C for 12 h. [b] Reaction performed using 16 equivalents of HFIP, PhMe (0.2 M), and heated at 100 °C for 24 h.

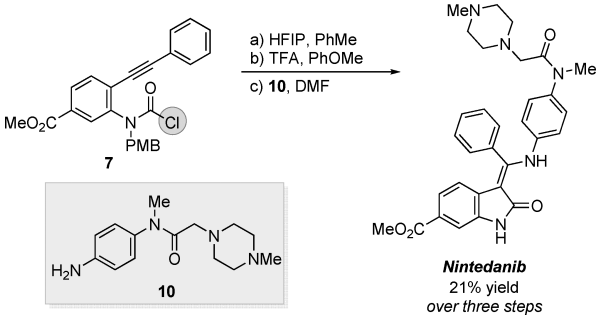


Scheme 3. Scale-up and derivatization studies of **2a**. Values represent isolated yields. Isomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixture. Stereochemistry determined via 1D and 2D-NOESY experiments.

in alkene stereochemistry when *E*-chlorinated methylene oxindoles were reacted with amines.[6c] Finally, concomitant reduction of both the olefin and C–Cl σ-bond was performed via palladium-hydride catalysis, accessing oxindole **6** in 82 % yield. The alkene stereochemistry of all derivatization products was elucidated by 1D and 2D NOESY experiments.

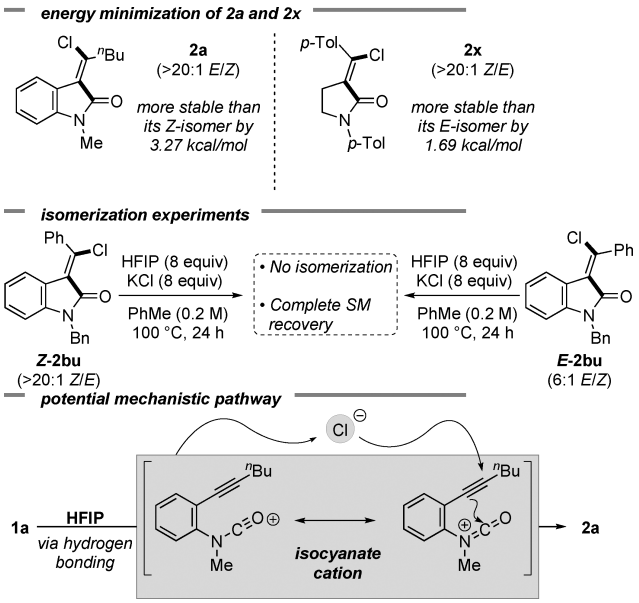
Following stereochemical confirmation of derivatization product ***Z*-3**, we sought to use the developed chloroacylation methodology alongside stereoinvertive C–N coupling for the synthesis of the medicinal agent, nintedanib (Scheme 4).[13] By subjecting alkyne-tethered carbamoyl chloride **7** to the reaction conditions, followed by PMB deprotection and condensation with aniline **10**, nintedanib was isolated in 21 % yield (unoptimized). Developed by Boehringer Ingelheim, nintedanib is used in the treatment of idiopathic pulmonary fibrosis and non-small-cell lung cancer under the brand names Ofev™ and Vargatef™.[14,15] Furthermore it has demonstrated potential as a treatment of pulmonary fibrosis associated with COVID-19 infection.[16] The developed synthetic route represents a unique disconnection of the oxindole moiety for the formation of this pharmaceutically relevant scaffold.[13,17]

Although HFIP has been employed in various processes such as substitutions, Friedel–Crafts alkylations and acyla-



Scheme 4. Synthesis of nintedanib. Reagents and conditions: a) HFIP, PhMe, 100 °C; b) TFA, PhOMe, 80 °C; c) **10**, DMF, 80 °C.

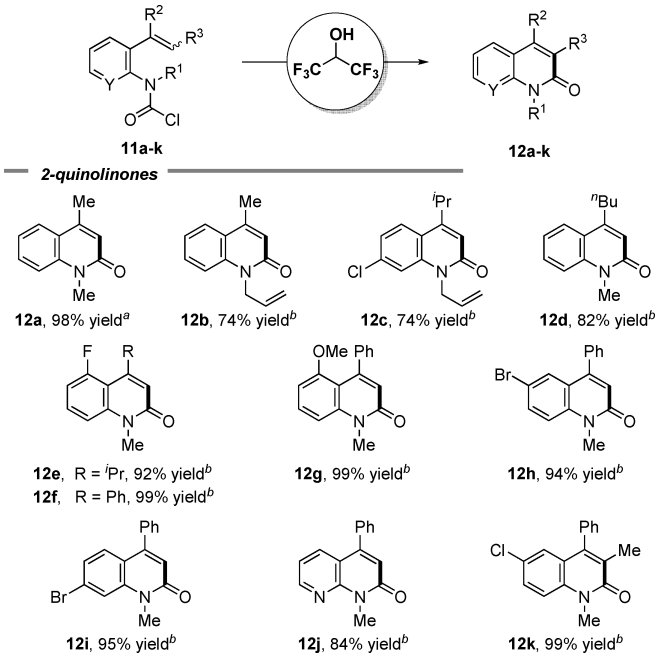
tions, and others,[12,18] its application in haloacylation reactions has not been described in the literature.[19] We performed DFT calculations (see supporting information for computational details) to obtain further insight on the stereoselective formation of methylene oxindole product **2a** (>20:1 *E*/*Z*) and methylene pyrrolidone **2x** (>20:1 *Z*/*E*). Ground-state analysis reveals that the products arising from these two substrate classes are each the thermodynamically favoured ones (Scheme 5). Additionally, we performed isomerization studies by independently reacting both *E*- and *Z*-isomers of substrate **2bu** with excess potassium chloride and HFIP.[11a] No isomerization was observed in either experiment, resulting in complete recovery of the starting material (See supporting information for additional isomerization and halide exchange experiments). These results indicate that methylene oxindole products are formed stereoselectively and irreversibly under the reaction conditions.[20]



Scheme 5. Computational and experimental mechanistic investigations.

A possible pathway for the formation of **2a** involves HFIP-assisted ionization of **1a** via a hydrogen bonding interaction to form an isocyanate cation intermediate, with concomitant release of chloride.[21,22] Addition of the latter across the alkyne in a *trans*-chloroacylation stereoselectively forms **2e** as its *E*-isomer. Methylene pyrrolidone product **2x** can be generated with complete Z-selectivity following formation of an isocyanate cation via two pathways: 1) *cis*-chloroacylation across the alkyne, or 2) *trans*-chloroacylation and subsequent isomerization. Additional studies are needed on this latter class of substrates for a more concrete mechanistic proposal.

We were intrigued to investigate the reactivity of carbamoyl chlorides bearing a tethered alkene. Reaction of substrate **11a** with HFIP furnished 2-quinolinone product **12a** in 98% yield through a vinylogous Friedel–Crafts reaction (Scheme 6). The 2-quinolinone motif has been



Scheme 6. Scope for the HFIP-assisted synthesis of 2-quinolinones. Reactions run on a 0.2 mmol scale. Values represent isolated yields of **12**. [a] Reaction performed using 8 equivalents of HFIP, PhMe (0.2 M), and heated for 16 h. [b] Reaction performed using 16 equivalents of HFIP, PhMe (0.2 M), and heated for 24 h.

applied in the synthesis of biologically active compounds and in materials science.[23] Various methods for their preparation have been previously described,[12,24] including a related report from the Takemoto group, who synthesized 2-quinolinones by heating alkene-tethered carbamoyl chlorides in NMP with catalytic HBr at 150 °C under microwave conditions.[25] We investigated the generality of the HFIP-promoted process, and soon discovered the need for a higher proportion of additive to obtain complete conversions. Using this method, **12b**–**12k** were obtained in yields ranging from 74% to 99%.

We have developed a metal-free, high yielding, and stereoselective synthesis of chlorinated methylene oxindoles and pyrrolidones using HFIP. This methodology was demonstrated in the synthesis of various derivatives including nintedanib. The application of alkene-tethered carbamoyl chlorides in an HFIP-assisted synthesis of 2-quinolinones was investigated. Additional experimental investigations to gain further mechanistic insight are currently underway in our laboratory.

Acknowledgements

We are grateful for financial support from the University of Toronto (U of T), the Natural Science and Engineering Research Council (NSERC), Alphora/Eurofins, and Kennarshore, Inc., for financial support. J.F.R thanks NSERC for graduate funding (PGS-D). A.Z. thanks NSERC for USRA funding. A.W. thanks the Walter C. Summer Memorial Fellowship and the Province of Ontario (QEII) for funding.

B.M. thanks NSERC for graduate funding (CGS-D). We thank A. D. Marchese (U of T) for substrates **11c** and **11e**. We thank I. Franzoni and J. Chen (U of T) for fruitful discussions. Computational studies were enabled in part through support provided by Compute Ontario (www.computeontario.ca) and Compute Canada (www.computecanada.ca). We thank Dr. Alan Lough (U of T) for X-ray crystallographic analysis. We thank Dr. Darcy Burns and Dr. Jack Sheng (U of T) for their assistance in NMR experiments.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: chloroacylation · cycloisomerization · HFIP · methylene oxindoles · stereoselectivity

[1] a) L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon, C. Tang, *J. Med. Chem.* **1998**, *41*, 2588 – 2603; b) S. Hauf, R. W. Cole, S. LaTerra, C. Zimmer, G. Schnapp, R. Walter, A. Heckel, J. van Meel, C. L. Rieder, J.-M. Peters, *J. Cell Biol.* **2003**, *161*, 281 – 294; c) F. Hilberg, G. J. Roth, M. Krssak, S. Kautschitsch, W. Sommergruber, U. Tontsch-Grunt, P. Garin-Chesa, G. Bader, A. Zoephel, J. Quant, A. Heckel, W. J. Rettig, *Cancer Res.* **2008**, *68*, 4774 – 4782.

[2] Selected examples: a) S. Lin, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 1967 – 1970; *Angew. Chem.* **2001**, *113*, 2021 – 2024; b) R. Yanada, S. Obika, T. Inokuma, K. Yanada, M. Yamashita, S. Ohta, Y. Takemoto, *J. Org. Chem.* **2005**, *70*, 6972 – 6975; c) R. Shintani, T. Yamagami, T. Hayashi, *Org. Lett.* **2006**, *8*, 4799 – 4801.

[3] Selected examples: a) A. Pinto, L. Neuville, P. Retailleau, J. Zhu, *Org. Lett.* **2006**, *8*, 4927 – 4930; b) B. M. Trost, N. Cramer, H. Bernsmann, *J. Am. Chem. Soc.* **2007**, *129*, 3086 – 3087; c) T. Miura, Y. Takahashi, M. Murakami, *Org. Lett.* **2008**, *10*, 1743 – 1745; d) H.-L. Wang, Z. Li, G.-W. Wang, S.-D. Yang, *Chem. Commun.* **2011**, *47*, 11336 – 11338; e) M. S. L. Kumar, S. K. Manna, S. Maji, G. Panda, *Org. Biomol. Chem.* **2017**, *15*, 1762 – 1766.

[4] a) M. R. Fielding, R. Grigg, C. J. Urch, *Chem. Commun.* **2000**, 2239 – 2240; b) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666 – 5667; c) S. Kamijo, Y. Sasaki, C. Kanazawa, T. Schüßeler, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 7718 – 7721; *Angew. Chem.* **2005**, *117*, 7896 – 7899.

[5] a) A. Pinto, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 3291 – 3295; *Angew. Chem.* **2007**, *119*, 3355 – 3359; b) T. Miura, T. Toyoshima, Y. Takahashi, M. Murakami, *Org. Lett.* **2009**, *11*, 2141 – 2143; c) S. Ueda, T. Okada, H. Nagasawa, *Chem. Commun.* **2010**, *46*, 2462 – 2464; d) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247 – 7290.

[6] a) E. M. Beccalli, A. Marchesini, T. Pilati, *Tetrahedron* **1994**, *50*, 12697 – 12712; b) M. S. C. Pedras, J. L. Sorensen, F. I. Okanga, I. L. Zaharia, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3015 – 3020; c) G. Cantagrel, B. de Carné-Carnavalet, C. Meyer, J. Cossy, *Org. Lett.* **2009**, *11*, 4262 – 4265; d) M. Sassatelli, É. Debiton, B. Aboab, M. Prudhomme, P. Moreau, *Eur. J. Med. Chem.* **2006**, *41*, 709 – 716; e) F.-M. Liao, Z.-Y. Cao, J.-S. Yu, J. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 2459 – 2463; *Angew. Chem.* **2017**, *129*, 2499 – 2503; f) A. D. Marchese, E. M. Larin, B. Mirabi, M. Lautens, *Acc. Chem. Res.* **2020**, *53*, 1605 – 1619.

[7] S. Tang, Q.-F. Yu, P. Peng, J.-H. Li, P. Zhong, R.-Y. Tang, *Org. Lett.* **2007**, *9*, 3413 – 3416.

[8] a) C. M. Le, X. Hou, T. Sperger, F. Schoenebeck, M. Lautens, *Angew. Chem. Int. Ed.* **2015**, *54*, 15897 – 15900; *Angew. Chem.* **2015**, *127*, 16127 – 16131; b) R. K. Shukla, K. Pal, C. M. R. Volla, *Chem. Asian J.* **2018**, *13*, 2435 – 2439; c) D. He, L. Huang, J. Li, W. Wu, H. Jiang, *Org. Lett.* **2019**, *21*, 8308 – 8311.

[9] For reviews on palladium-catalyzed C-X bond-forming reductive elimination: a) D. A. Petrone, C. M. Le, S. G. Newman, M. Lautens in *New Trends in Cross-Coupling: Theory and Application*, *Vol. 1* (Ed.: T. Colacot), RSC, Cambridge, **2015**, pp. 276 – 321; b) D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003 – 8104; c) D. J. Jones, M. Lautens, G. P. McGlacken, *Nat. Catal.* **2019**, *2*, 843 – 851.

[10] Selected examples: a) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 1232 – 1233; b) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 1778 – 1780; c) C. M. Le, P. J. C. Menzies, D. A. Petrone, M. Lautens, *Angew. Chem. Int. Ed.* **2015**, *54*, 254 – 257; *Angew. Chem.* **2015**, *127*, 256 – 259; d) D. A. Petrone, I. Franzoni, J. Ye, J. F. Rodríguez, A. I. Poblador-Bahamonde, M. Lautens, *J. Am. Chem. Soc.* **2017**, *139*, 3546 – 3557; e) Y. H. Lee, B. Morandi, *Angew. Chem. Int. Ed.* **2019**, *58*, 6444 – 6448; *Angew. Chem.* **2019**, *131*, 6510 – 6515; f) Y.-L. Sun, X.-B. Wang, F.-N. Sun, Q.-Q. Chen, J. Cao, Z. Xu, L.-W. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6747 – 6751; *Angew. Chem.* **2019**, *131*, 6819 – 6823; g) Z.-M. Zhang, B. Xu, L. Wu, L. Zhou, D. Ji, Y. Liu, Z. Li, J. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 8110 – 8115.

[11] a) C. M. Le, T. Sperger, R. Fu, X. Hou, Y. H. Lim, F. Schoenebeck, M. Lautens, *J. Am. Chem. Soc.* **2016**, *138*, 14441 – 14448; b) T. Sperger, C. M. Le, M. Lautens, F. Schoenebeck, *Chem. Sci.* **2017**, *8*, 2914 – 2922.

[12] For selected reviews on fluorinated alcohols as solvents and promoters in synthesis: a) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18 – 29; b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, 2925 – 2943; c) T. Sugiishi, M. Matsugi, H. Hamamoto, H. Amii, *RSC Adv.* **2015**, *5*, 17269 – 17282; d) S. Khaksar, *J. Fluorine Chem.* **2015**, *172*, 51 – 61; e) J. Wencel-Delord, F. Colobert, *Org. Chem. Front.* **2016**, *3*, 394 – 400; f) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088; g) X.-D. An, J. Xiao, *Chem. Rec.* **2020**, *20*, 142 – 161.

[13] a) A. Heckel, G. J. Roth, R. Walter, J. Van Meel, N. Redemann, U. Tontsch-Grunt, W. Spevak, F. Hilberg, WO2001027081A1, **2001**; b) G. J. Roth, A. Heckel, R. Walter, J. Van Meel, N. Redemann, U. Tontsch-Grunt, W. Spevak, F. Hilberg, US6762180B1, **2004**; c) G. J. Roth, A. Heckel, F. Colbatzky, S. Handschuh, J. Kley, T. Lehmann-Lintz, R. Lotz, U. Tontsch-Grunt, R. Walter, F. Hilberg, *J. Med. Chem.* **2009**, *52*, 4466; d) M. Lautens, J. F. Rodríguez, J. Bajohr (University of Toronto) Disclosure 10004072, **2021**.

[14] I. A. Dimitroulis, *Resp. Care* **2014**, *59*, 1450 – 1455.

[15] C. Rolfo, L. E. Raez, G. Bronte, E. S. Santos, K. Papadimitriou, L. Buffoni, J. P. van Meerbeeck, A. Russo, *Expert Opin. Invest. Drugs* **2013**, *22*, 1081 – 1088.

[16] a) E. Weisberg, A. Parent, P. L. Yang, M. Sattler, Q. Liu, Q. Liu, J. Wang, C. Meng, S. J. Buhrlage, N. Gray, J. D. Griffin, *Pharm. Res.* **2020**, *37*, 167; b) K. Lechowicz, S. Drożdżal, F. Machaj, J. Rosik, B. Szostak, M. Zegan-Barańska, J. Biernawska, W. Dabrowski, I. Rotter, K. Kotfis, *J. Clin. Med.* **2020**, *9*, 1917.

[17] a) J. Merten, G. Linz, J. Schnaubelt, R. Schmid, W. Rall, S. Renner, C. Reichel, R. Schiffers, WO2009071523A1, **2009**; b) L. Meca, WO2017016530A1, **2017**; c) V. Arava, S. Gogireddy, *Synth. Commun.* **2017**, *47*, 975 – 981.

[18] Selected examples: a) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff, C. R. Carson, *J. Am. Chem. Soc.* **2011**, *133*, 7688 – 7691; b) L. Dumitrescu, K. Azzouzi-Zriba, D. Bonnet-Delpon, B. Crousse, *Org. Lett.* **2011**, *13*, 692 – 695; c) P. A. Champagne, Y. Benhassine, J. Desroches, J.-F. Paquin, *Angew. Chem. Int. Ed.* **2014**, *53*, 13835 – 13839; *Angew. Chem.* **2014**, *126*, 14055 – 14059; d) R.-J.

Tang, T. Milcent, B. Crousse, *RSC Adv.* **2018**, *8*, 10314 – 10317; e) Y. Zhu, I. Colomer, T. J. Donohoe, *J. Am. Chem. Soc.* **2019**, *141*, 6489 – 6493; f) C. Qi, G. Force, V. Gandon, D. Leboeuf, *Angew. Chem. Int. Ed.* **2021**, *60*, 946 – 953; *Angew. Chem.* **2021**, *133*, 959 – 966.

[19] Selected examples of chloroacylation of π-bonds: a) M. Suda, *Tetrahedron Lett.* **1980**, *21*, 2555 – 2556; b) Y. Li, H. Matsumura, M. Yamanaka, T. Takahashi, *Tetrahedron* **2004**, *60*, 1393 – 1400; c) R. Hua, S.-Y. Onozawa, M. Tanaka, *Chem. Eur. J.* **2005**, *11*, 3621 – 3630; d) R. Cano, M. Yus, D. J. Ramón, *Tetrahedron* **2013**, *69*, 7056 – 7065; e) C. Chen, J.-C. Kang, C. Mao, J.-W. Dong, Y.-Y. Xie, T.-M. Ding, Y.-Q. Tu, Z.-M. Chen, S.-Y. Zhang, *Green Chem.* **2019**, *21*, 4014 – 4019; f) Z. Lei, A. Banerjee, E. Kusevska, E. Rizzo, P. Liu, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2019**, *58*, 7318 – 7323; *Angew. Chem.* **2019**, *131*, 7396 – 7401; g) Q.-S. Zhao, G.-Q. Xu, H. Liang, Z.-Y. Wang, P.-F. Xu, *Org. Lett.* **2019**, *21*, 8615 – 8619; h) D. V. Patil, H. Y. Kim, K. Oh, *Org. Lett.* **2020**, *22*, 3018 – 3022.

[20] Isomerization experiments using substrates **2v** and **2w** indicate some isomerization can occur under the reaction conditions. This result likely arises due to the presence of electron-donating or electron-withdrawing substituents in the aryl moiety, and thus it is substrate dependent (see supporting information).

[21] a) H. K. Hall, C. H. Lueck, *J. Org. Chem.* **1963**, *28*, 2818 – 2825; b) C. Jouitteau, P. L. Perchec, A. Forestière, B. Silicon, *Tetrahedron Lett.* **1980**, *21*, 1719 – 1722; c) E. K. Raja, S. O. Nilsson Lill, D. A. Klumpp, *Chem. Commun.* **2012**, *48*, 8141 – 8143; d) A. Sumita, H. Kurouchi, Y. Otani, T. Ohwada, *Chem. Asian J.* **2014**, *9*, 2995 – 3004.

[22] a) H. F. Motiwala, R. H. Vekariya, J. Aubé, *Org. Lett.* **2015**, *17*, 5484 – 5487; b) R. H. Vekariya, J. Aubé, *Org. Lett.* **2016**, *18*, 3534 – 3537.

[23] a) P. R. Angibaud, M. G. Venet, W. Filliers, R. Broeckx, Y. A. Ligny, P. Muller, V. S. Poncelet, D. W. End, *Eur. J. Org. Chem.* **2004**, 479 – 486; b) P. Cheng, Q. Zhang, Y.-B. Ma, Z.-Y. Jiang, X.-M. Zhang, F.-X. Zhang, J.-J. Chen, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3787 – 3789; c) S. Helmstetter, T. Badur, N. Hampp, *J. Polym. Res.* **2016**, *23*, 249.

[24] Selected examples: a) J. Ferguson, F. Zeng, N. Alwis, H. Alper, *Org. Lett.* **2013**, *15*, 1998 – 2001; b) D. Liang, Z. Hu, J. Peng, J. Huang, Q. Zhu, *Chem. Commun.* **2013**, *49*, 173 – 175; c) V. Rajeshkumar, T.-H. Lee, S.-C. Chuang, *Org. Lett.* **2013**, *15*, 1468 – 1471; d) Z. Zhang, L.-L. Liao, S.-S. Yan, L. Wang, Y.-Q. He, J.-H. Ye, J. Li, Y.-G. Zhi, D.-G. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 7068 – 7072; *Angew. Chem.* **2016**, *128*, 7184 – 7188; e) A. K. Kabi, R. Gujjarappa, N. Vodnala, D. Kaldhi, T. Ujjawal, K. Mukherjee, C. C. Malakar, *Tetrahedron Lett.* **2020**, *61*, 152535.

[25] Y. Yasui, I. Kakinokihara, H. Takeda, Y. Takemoto, *Synthesis* **2009**, 3989 – 3993.

[26] Deposition Numbers 2062479 (for **2x**) and 2062480 (for **2w**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: March 7, 2021
Revised manuscript received: May 24, 2021
Accepted manuscript online: June 22, 2021
Version of record online: July 16, 2021

