ChemPubSoc Europe

DOI: 10.1002/chem.201600649

CHEMISTRY
A European Journal
Communication

Synthetic Methods

Catalytic Enantioselective Synthesis of Halocyclopropanes

Amandine Pons,[a] Pavel Ivashkin,[a] Thomas Poisson,[a] André B. Charette,[b] Xavier Pannecoucke,[a] and Philippe Jubault*[a]

Abstract: A catalytic asymmetric synthesis of halocyclopropanes is described. The developed method is based on a carbenoid cyclopropanation of 2-haloalkenes with *tert*-butyl α-cyano-α-diazoacetate using a chiral rhodium catalyst that permits access to a broad range of highly functionalized chiral halocyclopropanes (F, Cl, Br, and I) in good yields, moderate diastereoselectivity, and excellent enantiomeric ratios. The reported methodology represents the first general catalytic enantioselective approach to halocyclopropanes.

The cyclopropane motif fascinates organic chemists, in fact this intriguing and smallest cycloalkane is present in a phalanx of natural and non-natural bioactive molecules.[1] This important constrained unit has been applied to alter both the metabolic stability and bioavailability of pharmacologically active molecules. Due to this, there has been interest in developing new approaches to synthesize this key structural motif. Moreover, the enantioselective and more particularly the catalytic enantioselective synthesis of cyclopropanes has received much attention.[2] Quite surprisingly, despite the advances made in that field, the catalytic asymmetric synthesis of halocylopropanes remains underexplored. This statement is in sharp contrast with the high synthetic value of halocylopropane scaffolds. Indeed, although fluorocyclopropanes are of interest for incorporation in bioactive compounds,[3] chloro-, bromo- and iodocyclopropanes are considered as versatile building blocks for the construction of complex molecular architectures. Most of the depicted approaches to access chiral halocyclopropanes require the use of a stoichiometric amount of chiral inductors,[4] whereas their catalytic asymmetric synthesis remains limited to few examples.[5] Regarding the catalytic enantioselective synthesis of chloro- and bromocyclopropanes, a Michael-initiated cyclopropanation reaction catalyzed by the oxazaborolidinium ion was reported by Hwang and Ryu[5a,b] (Figure 1), and a catalytic intramolecular cyclopropanation was independently reported by one of us[5c] and Nakada.[5d] Finally, the catalytic enantioselective synthesis of fluorocyclopropanes was investigated by Haufe and others, even though the scope

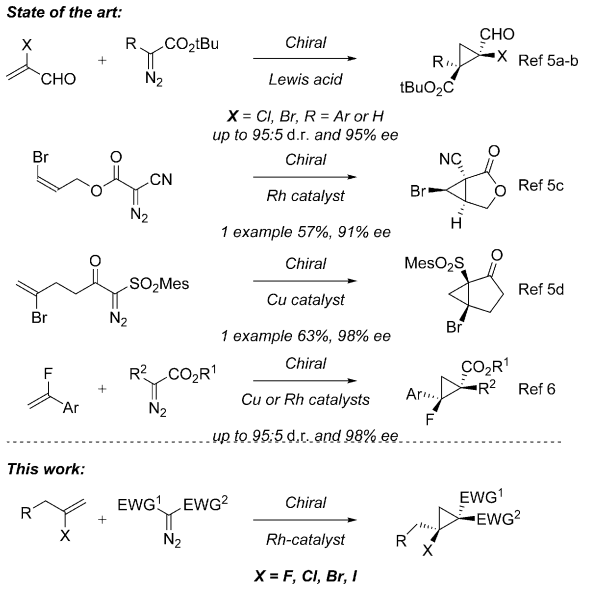


Figure 1. Previous work.

of the reaction remained limited to α-fluorostyrene derivatives.[6] To our knowledge, a single example of catalytic enantioselective synthesis of iodocyclopropanes has been recently reported.[5b] Basically, no general catalytic asymmetric process allowing the synthesis of halocyclopropanes with a broad substrate scope and high enantioselectivity has been reported to date. As part of our ongoing research program focusing on the development of straightforward access to halogenated cyclopropanes,[7] we envisioned the development of a catalytic asymmetric route to halocyclopropanes by developing a Rh-catalyzed asymmetric cyclopropanation of haloalkenes.

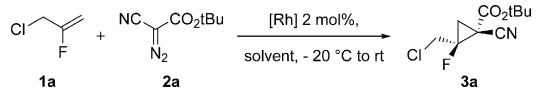
Initially, we investigated the Rh-catalyzed asymmetric cyclopropanation of fluoroalkene **1a** with *tert*-butyl α-cyano-diazoacetate (**2a**; Table 1). Initial attempts were devoted to select the optimal chiral catalyst to promote the cyclopropanation of **1a**. Catalyst $[Rh_2\{(S)\text{-NTTL}\}_4]$ was tested giving the fluorocyclopropane **3a** in 68% yield and good diastereoisomeric ratio (d.r.), albeit with poor enantioselectivities (entry 1), whereas $[Rh_2\{(S)\text{-TCPTTL}\}_4]$ furnished **3a** in similar yield and d.r. with a slight enhancement of the enantioselectivity (entry 2). To our

[a] A. Pons, Dr. P. Ivashkin, Dr. T. Poisson, Prof. Dr. X. Pannecoucke, Prof. Dr. P. Jubault
Normandie Univ., COBRA, UMR 6014 et FR 3038
Univ. Rouen, INSA Rouen, CNRS
1 rue Tesnière, 76821 Mont Saint-Aignan Cedex (France)
E-mail: philippe.jubault@insa-rouen.fr

[b] Prof. Dr. A. B. Charette
Centre in Green Chemistry and Catalysis, Faculty of Arts and Sciences
Department of Chemistry, Université de Montréal
PO Box 6128, Station Downtown, Montréal, Québec, H3C 3J7 (Canada)

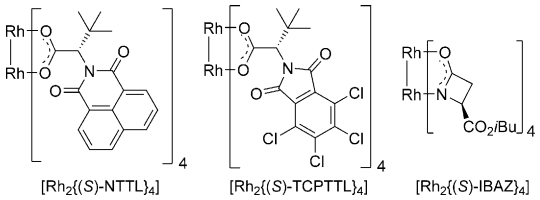
Supporting information for this article can be found under http://dx.doi.org/10.1002/chem.201600649.

Table 1. Optimization study.[a]



1a 2a 3a

Entry	[Rh][b]	Solvent	Yield [%][c]	d.r.[d]	*ee*[e]
1	$[Rh_2\{(S)\text{-NTTL}\}_4]$	DCM	71	32:68	8/7
2	$[Rh_2\{(S)\text{-TCPTTL}\}_4]$	DCM	68	28:72	39/11
3	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	DCM	51	76:24	95/85
4[f]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	DCM	56	75:25	95/86
5[g]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	DCM	63	76:24	96/88
6[g]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	toluene	58	64:36	96/90
7[g]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	THF	42	65:35	97/91
8[g]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	CPME	63	61:39	97/92
9[g,h]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	DCM	57	62:38	93/81
10[g,i]	$[Rh_2\{(S)\text{-IBAZ}\}_4]$	DCM	58	74:26	95/86

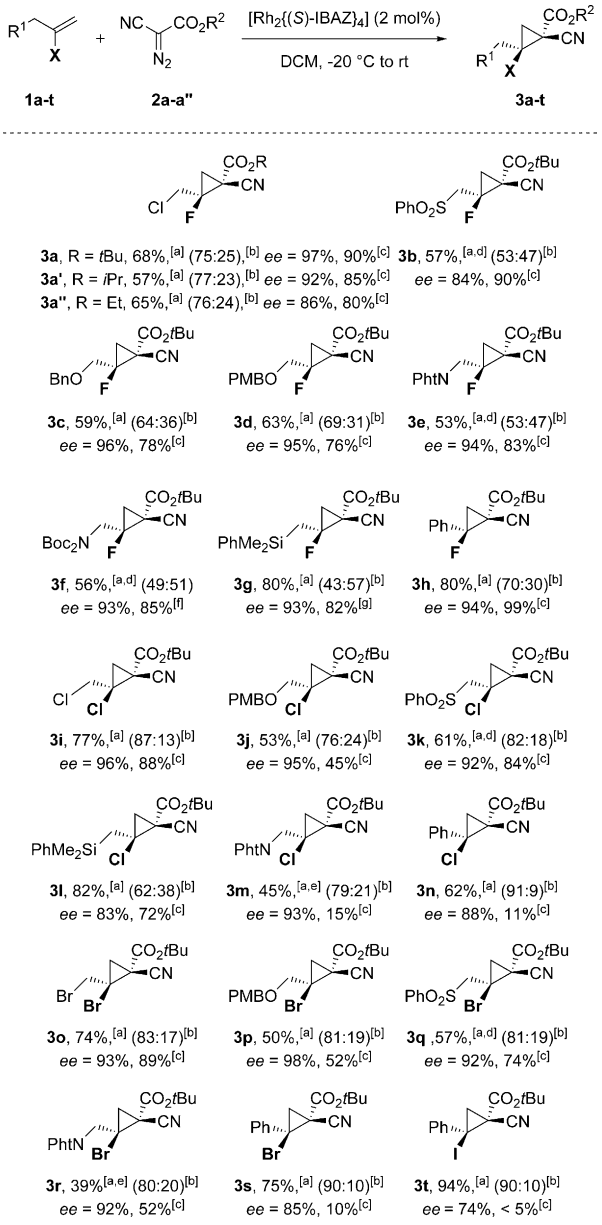


$[Rh_2\{(S)\text{-NTTL}\}_4]$ $[Rh_2\{(S)\text{-TCPTTL}\}_4]$ $[Rh_2\{(S)\text{-IBAZ}\}_4]$

[a] **1a** (2 equiv), **2a** (1 equiv), [Rh] (2 mol%), and solvent (0.2 M), −20 °C to rt. [b] See the Supporting Information for detailed names. [c] Isolated yields. [d] Diastereoisomeric ratio (*trans*:*cis*) determined by ^{19}F NMR on the crude reaction mixture. [e] Enantiomeric excess (*trans*/*cis*) determined by GC analysis on a chiral stationary phase. [f] [**2a**] = 1 M. [g] [**2a**] = 2 M. [h] Reaction was performed at rt. [i] Addition of **2a** was performed at 0 °C. CPME = cyclopentyl methyl ether.

delight, the use of $[Rh_2\{(S)\text{-IBAZ}\}_4]$[8] allowed the formation of **3a** in 51% yield, 76:24 diastereoisomeric ratio, and excellent enantioselectivities for both diastereoisomers (95% and 85%, entry 3). To improve the conversion into **3a**, the concentration of **2a** was studied, leading an optimal 2 M concentration, giving **3a** in 63% isolated yield along with a similar d.r. and no alteration of the enantioselectivities (entries 4 and 5). A solvent survey revealed that dichloromethane (DCM) was the most appropriate solvent to ensure decent diastereoselectivities and excellent enantiomeric excess (entries 5–8). The temperature of the reaction was then examined, and the addition of **2a** performed at −20 °C gave the best results since no improvement of the reaction yield nor the diastereo- and enantioselectivities was detected (entries 9 and 10).

With the optimal set of conditions in hand (Table 1, entry 5), we sought to extend the scope of the reaction to several fluorinated and halogenated olefins (Scheme 1). First, we examined the influence of the steric demand of diazo derivatives. A screening of *tert*-butyl, isopropyl, and ethyl ester derivatives was performed. Steric hindrance of the diazo derivative had little effect on the diastereoselectivity of the reaction. However, a slight decrease of the enantioselectivity was noticed since the best *ee*'s were obtained with **2a** as a reaction partner. We then turned our attention to the synthesis of various enantioenriched fluorocyclopropanes. When **1b** was used, the corresponding fluorocyclopropane **3b** was obtained in 57% yield, 57:43 d.r., and excellent enantioselectivities for both diastereo-



Scheme 1. Scope of the reaction. [a] Isolated yield (mixture of diastereoisomers). [b] Diastereoisomeric ratio (*trans*:*cis*). [c] Determined by HPLC or GC analysis on a chiral stationary phase (*trans*/*cis*). [d] [**2**] = 1 M. [e] [**2**] = 0.5 M. [f] Determined by ^{19}F NMR using $Eu(hfc)_3$ as a chiral agent after chemical transformation, see the Supporting Information for details. [g] Determined by GC on a chiral stationary phase (*trans*/*cis*) after Tamao–Fleming oxidation.

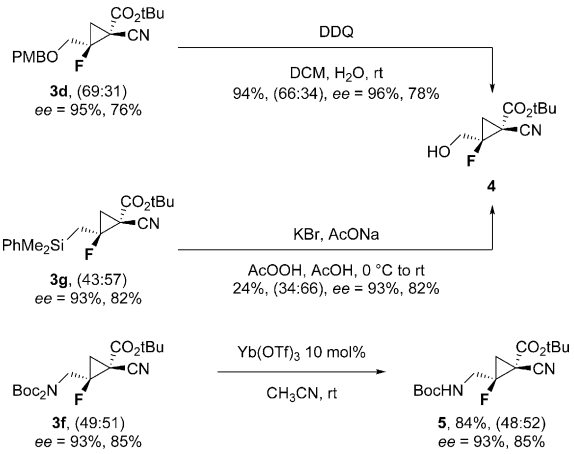
isomers, 84% and 90%, respectively. The X-ray crystallographic analysis of both diastereoisomers, separated by flash chromatography, led us to determine unambiguously the relative and absolute configuration of each diastereoisomer.[9,10,11] As it is typically observed in rhodium carbene chemistry, the formation of the major diastereomer resulted from an attack of the rhodium carbene on the pro-*S* face of the alkene, whereas the other diastereomer was generated by an attack on the opposite enantiotopic face (pro-*R*). Then, the process was extended to olefins **1c** and **1d** and the corresponding fluorocyclopropanes **3c** and **3d**, respectively, were isolated in good yields, moderate diastereoselectivities, and excellent enantioselectivi-

ties. *N*-Protected olefins **1e** and **1f** reacted smoothly under our conditions furnishing *N*-phthalimide **3e** and bis-*N*-Boc-protected fluorocyclopropanes **3f**, respectively, in decent yields and excellent enantioselectivities for both diastereoisomers.

Fluoroallylsilane **1g** was reacted under our standard conditions and the resulting fluorocyclopropane **3g** was obtained in 80% isolated yield with a reverse diastereoselectivity and excellent enantiomeric excesses. Finally, fluorostyrene derivative **1h** was tested, yielding fluorocyclopropanes **3h** in good yield with 70:30 diastereoisomeric ratio and an excellent enantiomeric excess for each diastereoisomer. Encouraged by these promising results using fluorinated olefins, we turned our attention to the chlorinated substrates. Similarly, the asymmetric cyclopropanation reaction proceeded well along with a good functional group tolerance. Indeed, chlorinated olefins bearing halogen, O-protected alcohol, sulfone, silyl group, N-protected amine, or phenyl substituents reacted smoothly. The corresponding highly functionalized chlorocyclopropanes **3i–n** were obtained in moderate to good yields and good to excellent diastereoselectivities. Note that diastereoselectivities are generally higher with chlorinated olefins than their fluorinated analogues. In all cases, the enantiocontrol of the reaction was excellent for the major diastereoisomer (up to 96% *ee*). Regarding olefins, **1m** and **1n**, a significant drop of the enantiomeric ratio was measured on the minor diastereoisomer since the latter was obtained with less than 15% *ee*. Subsequently, we studied the bromo-substituted olefins **1o–s** to extend the versatility of our methodology. To our delight, our reaction conditions were compatible with various functional groups, such as halogen, benzyl ether, sulfone, phthalimides, and aryl substituent. Good levels of diastereocontrol were observed and excellent enantioselectivities were measured for the major diastereoisomers. Finally, in order to compare the effect of the halogen atom on the stereochemical outcome of the reaction, α-iodo styrene **1t** was tested. The corresponding iodocyclopropane **3t** was isolated in 94% yield as a 90:10 diastereoisomeric ratio and 74% *ee* of the major isomer. Interestingly, the enantioselectivity of the reaction decreased in the order: F > Cl > Br > I. Indeed, the enantiomeric excess of the major isomer slightly decreased, whereas the minor isomer was almost obtained as a racemic mixture with α-chloro (**3n**), -bromo (**3s**) and -iodo styrenes (**3t**). In contrast the diastereoselectivity of the reaction is higher with chlorinated, brominated, and iodinated olefins compared to the fluorinated ones.

The versatility of the resulting halocyclopropanes can be illustrated by their further functionalization (Scheme 2). We first demonstrated that the *p*-methoxybenzyl (PMB) protecting group can be readily removed from compound **3d**, giving **4** in 94% isolated yield.[11] In addition, silylated cyclopropane **3g** can be converted into **4** through a Tamao–Fleming oxidation without loss of the enantiomeric excess. Then, the Yb-catalyzed selective removal of one Boc protecting group was performed giving **5** in 84% isolated yield.

In summary, we reported in this communication the first general method to access highly functionalized halocyclopropanes starting from readily available haloalkenes and functionalized diazo derivatives in the presence of $[Rh_2\{(S)\text{-IBAZ}\}_4]$ as a catalyst. The corresponding cyclopropanes were obtained in good yields and moderate to good diastereoselectivities. Both diastereoisomers were generally obtained with excellent enantiomeric excess. The scope of the reaction was successfully extended to a broad range of functionalized olefins, highlighting the high functional group tolerance of the method, giving access to highly decorated halocyclopropanes. Finally, the versatility of these halocyclopropanes was demonstrated in the course of functional group manipulations.



Scheme 2. Synthetic utility of the products.

Acknowledgements

This work was partially supported by INSA Rouen, Rouen University, CNRS, EFRD, Labex SynOrg (ANR-11-LABX-0029), and Région Haute-Normandie (CrunchNetwork). A.P. thanks the Labex SynOrg for a doctoral fellowship. P.I. thanks the IS:CE-Chem project and Interreg IV: A France-(Channel)-England Program for a doctoral fellowship. A.B.C. thanks the Labex SynOrg (ANR-11-LABX-0029) for a chair of excellence.

Keywords: asymmetric catalysis · chiral rhodium catalyst · cyclopropane · diazo derivatives · fluorine

[1] a) R. Faust, *Angew. Chem. Int. Ed.* **2001**, *40*, 2251–2253; *Angew. Chem.* **2001**, *113*, 2312–2314; b) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589–8627; c) A. de Meijere, *Top. Curr. Chem.* **2000**, *207*, 1–227; d) D. Y. K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631.

[2] H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050.

[3] For a review, see: E. David, G. Milanole, P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Chem. Eur. J.* **2012**, *18*, 14904–14917.

[4] For selected examples of fluorocyclopropanes, see: a) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, *Tetrahedron Lett.* **1992**, *33*, 3487–3490; b) L.-P. B. Beaulieu, J. F. Schneider, A. B. Charette, *J. Am. Chem. Soc.* **2013**, *135*, 7819–7822; c) X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 6966–6970; *Angew. Chem.* **2012**, *124*, 7072–7076; d) P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Org. Lett.* **2012**, *14*, 5130–5133; e) C. Navuluri, A. B. Charette, *Org. Lett.* **2015**, *17*, 4288–4291; For selected examples of chlorocyclopropanes, see: f) L.-P. B. Beaulieu, L. E. Zimmer, A. Gagnon, A. B. Charette, *Chem. Eur. J.* **2012**, *18*, 14784–14791; For selected example of bromocyclopropanes, see: g) H. Y. Kim, L. Salvi, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 954–962. For selected examples of iodocy-

clopropanes, see: h) H. Y. Kim, A. E. Lurain, P. García-García, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 13138 – 13139; i) L.-P. B. Beaulieu, L. E. Zimmer, A. B. Charette, *Chem. Eur. J.* **2009**, *15*, 11829 – 11832; j) L. E. Zimmer, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 15624 and ref. [4g].

[5] a) L. Gao, G.-S. Hwang, D. H. Ryu, *J. Am. Chem. Soc.* **2011**, *133*, 20708 – 20711; b) S. Y. Shim, J. Y. Kim, M. Nam, G.-S. Hwang, D. H. Ryu, *Org. Lett.* **2016**, *18*, 160 – 163; c) W. Lin, A. B. Charette, *Adv. Synth. Catal.* **2005**, *347*, 1547 – 1552; d) M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 2860 – 2861.

[6] a) S. Hruschka, R. Fröhlich, P. Kirsch, G. Haufe, *Eur. J. Org. Chem.* **2007**, 141 – 148; b) O. G. Meyer, R. Fröhlich, G. Haufe, *Synthesis* **2000**, 1479 – 1490. For an extension of the reaction scope, see: c) Y. Su, M. Bai, J. B. Qiao, X. J. Li, R. Li, Y. Q. Tu, P. Gu, *Tetrahedron Lett.* **2015**, *56*, 1805 – 1807.

[7] a) P. Ivashkin, G. Lemonnier, A. S. Tora, J.-P. Pin, C. Goudet, P. Jubault, X. Pannecoucke, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2523 – 2526; b) G. Milanole, S. Couve-Bonnaire, J.-F. Bonfanti, P. Jubault, X. Pannecoucke, *J. Org. Chem.* **2013**, *78*, 212 – 223; c) G. Milanole, F. Andriessen, G. Lemonnier, M. Sebban, G. Coadou, S. Couve-Bonnaire, J.-F. Bonfanti, P. Jubault, X. Pannecoucke, *Org. Lett.* **2015**, *17*, 2968 – 2971; d) A. Pons, H. Beucher, P. Ivashkin, G. Lemonnier, T. Poisson, A. B. Charette, P. Jubault, X. Pannecoucke, *Org. Lett.* **2015**, *17*, 1790 – 1793; e) T. Ferrary, E. David, G. Milanole, T. Besset, P. Jubault, X. Pannecoucke, *Org. Lett.* **2013**, *15*, 5598 – 5601; f) P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Org. Lett.* **2012**, *14*, 2270 – 2273; g) S. Taillemaud, N. Diercxsens, A. Gagnon, A. B. Charette, *Angew. Chem. Int. Ed.* **2015**, *54*, 14108 – 14112; *Angew. Chem.* **2015**, *127*, 14314 – 14318.

[8] V. N. G. Lindsay, D. Fiset, P. J. Gritsch, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* **2013**, *135*, 1463 – 1470.

[9] See the Supporting Information for details.

[10] The absolute configuration (*S*) of the carbon atom bearing ester and nitrile moieties remained unchanged in both diastereoisomers.

[11] CCDC 1445418 (*trans*-**3b**) and 1445417 (*cis*-**3b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre

[12] Note that both diastereoisomers can be readily separated at this stage by flash chromatography, see the Supporting Information for details.

Received: February 11, 2016
Published online on March 16, 2016