EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: [Cp*RhIII] in an Ionic Liquid as a Highly Efficient and Recyclable Catalytic Medium for Regio-and Diastereoselective Csp3-H Carbenoid Insertion

Authors: Jianglian Li, Lin Zhou, Yaoling Wang, Qiang Ma, Yuan Lei, Ruizhi Lai, Yi Luo, Li Hai, and Yong Wu

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901279

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901279

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

COMMUNICATION

[Cp*Rh^{III}] in an Ionic Liquid as a Highly Efficient and Recyclable Catalytic Medium for Regio-and Diastereoselective Csp^3-H Carbenoid Insertion

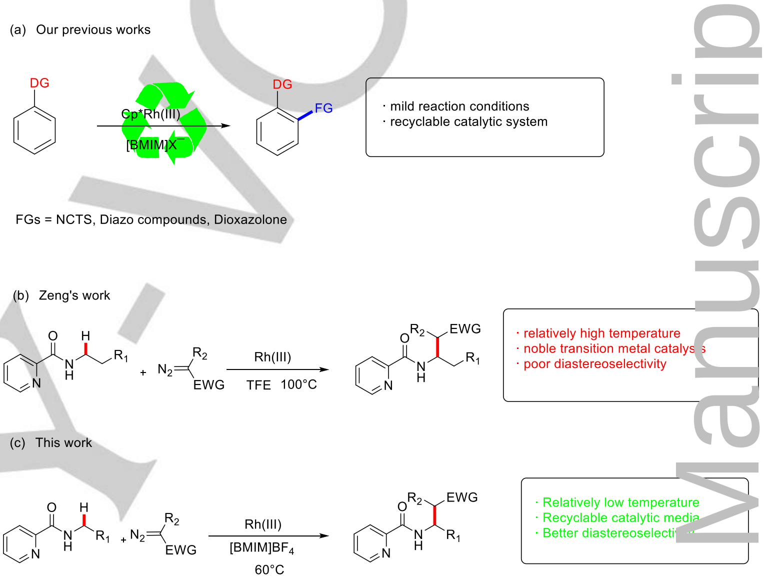
Jianglian Li, Lin Zhou, Yaoling Wang, Qiang Ma, Yuan Lei, Ruizhi Lai, Yi Luo, Li Hai* and Yong Wu*[a]

Abstract: Reported herein is a bidentate-assisted Csp^3-H bond insertion using Cp*Rh(III)/IL as a highly efficient and recyclable catalytic medium, and this methodology showed good functional group tolerance. Notably, the application of ionic liquid not only lowered the temperature, but also enhanced the diastereoselectivity. This work significantly expanded the scope of ionic liquids in Csp^3-H functionalizations

Introduction

In the past few decades, green chemistry, a relatively new emerging field, has received general interests due to the increased awareness of the environment issues worldwide.[1] In order to achieve the goal of green chemistry, chemists have been dedicated to optimizing the whole process of chemical reactions. While modern chemistry is heavily relied on the use of low polar, volatile and toxic organic solvents, which, unfortunately, accounts for the largest proportion in most reaction systems. Discovering alternative reaction mediums that are eco-friendly is one of the major focal point of green chemistry.[2]

Ionic liquids (ILs) have been increasingly used as recyclable solvents in both academic and industrial fields in recent years due to many advantages, such as the low toxicity, nonflammable, recyclable, excellent chemical and thermal stability, negligible vapor pressure as well as the good solubility for organic and inorganic compounds.[3] Rather intriguingly, the ability to recycle the catalysts makes ILs ideal substitutes for many volatile organic solvents in noble transition-metal catalyzed reactions, such as Suzuki couplings,[4] Michael additions,[5] Olefin metathesis,[6] C-H activations[7] and other reactions.[8] In addition, enhancing stereoselectivity is another promising feature of using ionic liquids as solvents, yet only a few types of reactions using chiral or non-chiral ILs have been reported,[8b, 9] Therefore, the development of more reaction types is still highly desirable. Most recently, our group successfully demonstrated the directing groups (DGs)-assisted C-H activations of using Cp*M(III)/ILs as recyclable catalytic media (scheme 1a).[7a, 7b, 7e] As a continuous research of our previous work, we envisage the possibility of using Cp*M(III)/ILs as recyclable catalytic media to enhance the stereoselectivity of the more challenging Csp^3-H bond functionalization.



Scheme 1. Related literature reports on Csp^2-H/ Csp^3-H functionalization

Transition-metal catalyzed heteroatom-adjacent Csp^3-H carbenoid insertions recently provide a new, atom-economic way to construct C-C bonds,[10] while substrate-specific obstacles prompt scientists to explore more effective approaches. In 2017, Zeng's group firstly reported a bidentate-assisted Rh(III)-catalyzed *N*-methylene Csp^3-H bond insertion (scheme 1b).[11] This strategy provides an effective approach to diverse β-amino esters, but has a limited practicality because of the poor diastereoselectivity and relatively high temperature. Herein, we demonstrate a mild and green method for Csp^3-H bond carbenoid insertion with good diastereoselectivity by constructing a highly efficient and recyclable catalytic medium using Cp*Rh(III)/IL (scheme 1c).

Results and Discussion

At the start of our investigation, N-butyl-pyridine-2-carboxylic acid amide (1a) was treated with [Cp*RhCl$_2$]$_2$ (5 mol%), AgOAc (20 mol%) and α-diazo-β-ketoester (**2a**) in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl) ([BMIM]NTf$_2$) at 100 °C for 24 h, and the desired product (**3a**) was obtained in 88% yield (Table 1 entry 1). Encouraged by this result, we had investigated other 1-butyl-3-methyl- imidazolium salts and found

---

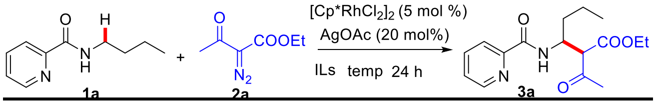
[a] J. Li, L. Zhou, Dr. Y. Wang, Q. Ma, Y. Lei, R. Lai, Y. Luo, Dr. L. Hai, Prof. Dr. Y. Wu*
Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry and Department of Medicinal Chemistry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy
Sichuan University
No. 17 Southern Renmin Road, Chengdu, Sichuan 610041, People's Republic of China.
E-mail: wyong@scu.edu.cn

10.1002/ejoc.201901279

that [BMIM]BF_4 gave the best result (Table 1, entries 2-6). The following screening of the catalysts and silver salts didn't increase the yield (see table S1). From our previous works,[7a, 7b, 7e] ionic liquids could reduce the reaction temperature, the effect of lowering temperatures on the reaction was evaluated. Delightingly, the yield and the d.r. value increased when the temperature was lowered to 60 °C compared with the original literature (entries 7-9). Whether reducing or increasing the loading of α-diazo-β-ketoester **2a**, catalysts and silver salts, the yields would decrease more or less (entries 10-14). Accordingly, the reaction condition was optimized to the following: **1a** (0.15 mmol), **2a** (0.225 mmol), [Cp*$RhCl_2$]$_2$ (5 mol%) and AgOAc (20 mol%) in 0.5 mL [BMIM]BF_4 at 60 °C for 24 h under Ar.

.

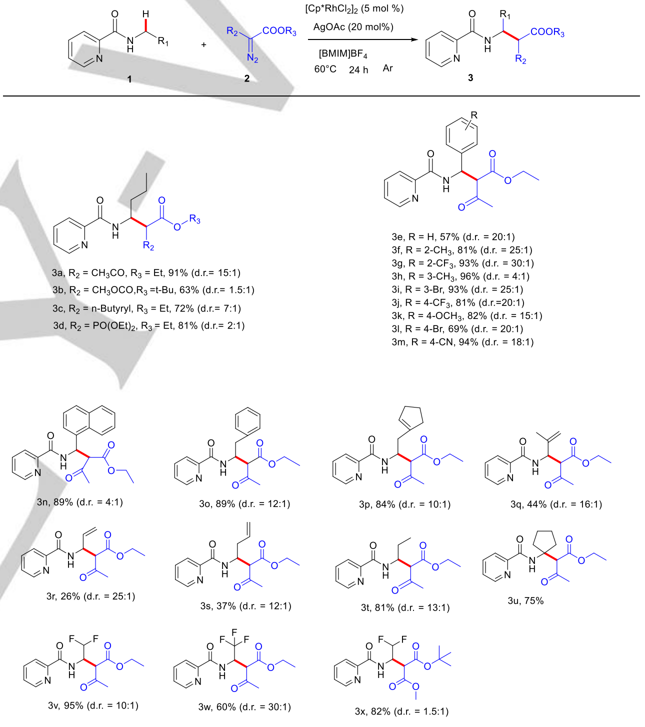
Table 1. Optimization of the reaction conditions.[a]



Entry	Temp (°C)	ILs	Yield (%)[b]	d.r. [c]
1	100	[BMIM]NTf_2	88	5:1
2	100	[BMIM]BF_4	93	8:1
3	100	[BMIM]PF_6	54	3:1
4	100	[BMIM]OAc	trace	-
5	100	[BMIM]SbF_6	73	4:1
6	100	[BDMIM]BF_4	81	6:1
7	80	[BMIM]BF_4	92	10:1
8	**60**	**[BMIM]BF_4**	**91**	**15:1**
9	40	[BMIM]BF_4	58	20:1
10[d]	60	[BMIM]BF_4	76	10:1
11[e]	60	[BMIM]BF_4	88	12:1
12[f]	60	[BMIM]BF_4	70	10:1
13[g]	60	[BMIM]BF_4	78	13:1
14[h]	60	[BMIM]BF_4	82	12:1

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.225 mmol), [Cp*$RhCl_2$]$_2$ (5 mol%) and AgOAc (20 mol%) in 0.5 mL solvent at specific temperature for 24 h under Ar. [b] Isolated yield by chromatography on silica gel. [c] d.r. values were determined by ^{1}H NMR spectroscopy. [d] [Cp*$RhCl_2$]$_2$ 3 mol%. [e] [Cp*$RhCl_2$]$_2$ 10 mol%. [f] AgOAc 10 mol%. [g] AgOAc 40 mol%. [h] **2a** 2.0 eq. Cp* = pentamethylcyclopentadieny; [BMIM] = 1-butyl-3-methylimidazolium; [MTMG] = N, N, N', N', N -pentamethyl-quinone.

With the optimized conditions in hand, we set out to explore the feasibility and generality of this approach (Scheme 2). A range of diazo compounds was first investigated and most of them gave moderate to excellent yields but poor diastereoselectivities (**3a-3d**). To our delight, when we studied *N*-benzyl-substituted substrates, electron-withdrawing and electron-donating groups at different positions on phenyl rings had little effect on the reaction. Besides, the yields and d.r. values were better than those in organic solvents (**3e-3m**). Therefore, we were also interested in the replacement of phenyl with naphthalene, and it failed to afford a good diastereoselectivity (**3n**). However, phenylethylamine-based amides could tolerate this reaction system smoothly (**3o**). To further evaluate the scope of this process, we then investigated some substrates with alkenyl groups. Unfortunately, most of them were not tolerated for this transformation well and gave low yields, except cyclopentene substrate (**3p-3s**). In addition, the naphthenic and shorter straight-chain alkylamine-based amides were amenable to the reaction with good to excellent d.r. values (**3t**, **3u**). Because of the widespread applications of organofluorine compounds in drug development,[12] the fluoroalkylamine-based amides were studied and proved to be compatible substrates (**3v-3x**).



Scheme 2. Substrate scope. Reaction conditions: **1a** (0.15 mmol), **2a** (0.225 mmol), [Cp*$RhCl_2$]$_2$ (5 mol%) and AgOAc (20 mol%) in 0.5 mL [BMIM]BF_4 at 60 °C for 24 h under Ar; isolated yield by chromatography on silica gel.; d.r. values were determined by ^{1}H NMR spectroscopy.

To further verify the recovery and applicability of this catalyst system, the recycling of the [Cp*Rh^{III}]/[BMIM]BF_4 system was investigated under the optimized condition with **1a** and **2a** as substrates. After completion, the crude product was simply separated by extraction. The organic layer was directly subjected to purification, and the ionic liquid layer was further subjected to vacuum to remove the remaining diethyl ether before it was reused in subsequent reactions (without adding fresh Rh catalyst). After they were reused five times, there was no notable loss of catalytic activity (Figure 1).

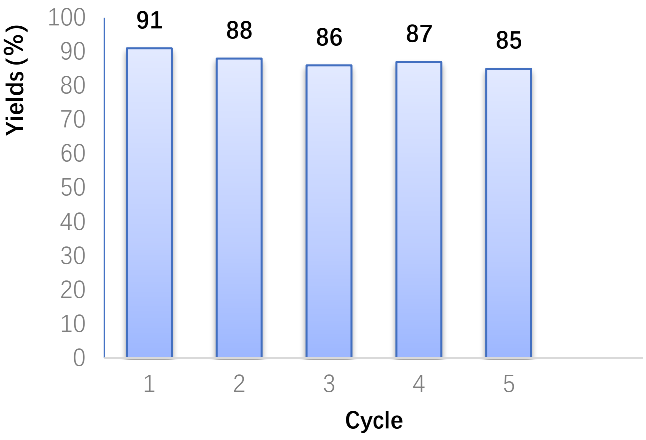


Figure 1. Recycling study results.

Structurally, ionic liquids are similar to *N*-heterocyclic carbenes (NHCs), which are outstanding nucleophilic catalysts in organic synthesis and electron-rich ligands in transition-metal-catalyzed transformations.[13] Among these reactions, free carbene is necessary because it can form complexes with metals, so we studied a 2-substituted ionic liquid and found that this procedure was still tolerated (Table 1, entry 6). This result indicated that ionic liquid we used may just act as solvent or PTC in this system. On the basis of the above results (Table 1, Entries 1-6) and previous reports, [9e, 9f] it seems that anions in ionic liquid play a crucial role as solvent in the stereoselectivity even though the effect was not very clear.

Conclusions

In summary, we have developed a recyclabe strategy of bidentate-assisted Csp^3-H carbenoid insertion using Cp*Rh(III)/IL catalytic medium with advantages of lower temperature and better diastereoselectivity. This procedure tolerates various kinds of amine-based substrates and provides an effective approach to diverse beta-amino esters. Moreover, this strategy could enrich the reaction types using ionic liquids as solvents, in which the stereoselectivities are enhanced. In terms of DG-assisted Csp^3-H functionalizations, we believe that this discovery would be conductive to more extensive use of ionic liquids as solvents for enhancing stereoselectivity.

Experimental Section

General procedure for the synthesis of 3a: To a test tube with a magnetic stir bar were added picolinamide **1a** (0.15 mmol), α-diazo-β-ketoester **2a** (0.225 mmol, 1.5 eq.), [Cp*RhCl$_2$]$_2$ (5 mol %), AgOAc (20 mol %) and [BMIM]BF$_4$ (0.5 mL) under Ar atmosphere. The reaction mixture was stirred at 60 °C for 24 h. Afterward, the mixture was extracted with diethyl ether (5 × 1mL). The organic solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography with petroleum/ethyl acetate as the eluent to afford the desired product.

Acknowledgements

We thank Prof. Yong Wu for helpful discussions and preliminary experiments. This work was supported by the National Natural Science Foundation of China (grant number 81573286, 81373259 and 81773577).

Conflict of interest

The authors declare no conflict of interest.

Keywords: Csp^3-H Carbenoid Insertion • diastereoselectivity • Ionic Liquids • Recyclable catalyst system

[1] a) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301-312; b) H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata, P. T. Anastas, *Green Chem.* **2018**, *20*, 1929-1961.

[2] T. Welton, *Proc. R. Soc. A* **2015**, *471*, 20150502.

[3] a) J. Dupont, R. F. de Souza, P. A. Z. Suarez, *Chem. Rev.* **2002**, *102*, 3667-3692; b) K. Ghandi, *Green Sustainable Chem.* **2014**, *04*, 44-53; c) J. P. Hallett, T. Welton, *Chem. Rev.* **2011**, *111*, 3508-3576; d) X. Han, D. W. Armstrong, *Org. Lett.* **2005**, *7*, 4205-4208; e) J. Li, S. Yang, W. Wu, H. Jiang, *Chem. Commun.* **2014**, *50*, 1381-1383; f) C. Maton, N. De Vos, C. V. Stevens, *Chem. Soc. Rev.* **2013**, *42*, 5963-5977; g) N. V. Plechkova, K. R. Seddon, *Chem. Soc. Rev.* **2008**, *37*, 123-150; h) H. M. Savanur, R. G. Kalkhambkar, K. K. Laali, *Appl. Catal., A* **2017**, *543*, 150-161; i) R. Sharma, M. Abdullaha, S. B. Bharate, *J. Org. Chem.* **2017**, *82*, 9786-9793; j) R. G. Soengas, V. L. M. Silva, J. Pinto, H. Rodríguez-Solla, A. M. S. Silva, *Eur. J. Org. Chem.* **2016**, *2016*, 99-107.

[4] a) F. Wang, S. Tang, H. Ma, L. Wang, X. Li, B. Yin, *Chin. J. Chem.* **2014**, *32*, 1225-1232; b) H. B. Wang, Y.-L. Hu, D.-J. Li, *J. Mol. Liq.* **2016**, *218*, 429-433.

[5] a）M. M. Dell' Anna, V. Gallo, P. Mastrorilli, C. F. Nobile, G. Romanazzi, G. P. Suranna, *Chem. Commun.* **2002**, 434-435; b）H. T. Yoshitaka Hamashima, Daido Hotta, and Mikiko Sodeoka, *Org. Lett.* **2003**, *5*, 3225-3228.

[6] P. Sledz, M. Mauduit, K. Grela, *Chem. Soc. Rev.* **2008**, *37*, 2433-2442.

[7] a) S. Lv, Y. Li, T. Yao, X. Yu, C. Zhang, L. Hai, Y. Wu, *Org. Lett.* **2018**, *20*, 4994-4997; b) Q. Ma, X. Yu, R. Lai, S. Lv, W. Dai, C. Zhang, X. Wang, Q. Wang, Y. Wu, *ChemSusChem* **2018**, *11*, 3672-3678; c) F. Mou, Y. Sun, W. Jin, Y. Zhang, B. Wang, Z. Liu, L. Guo, J. Huang, C. Liu, *RSC Adv.* **2017**, *7*, 23041-23045; d) S. B. Park, H. Alper, *Chem. Commun.* **2005**, 1315-1317; e) C. Zhang, X.-M. Chen, Y. Luo, J.-L. Li, M. Chen, L. Hai, Y. Wu, *ACS Sustainable Chem. Eng.* **2018**, *6*, 13473-13479.

[8] a) O. Basle, N. Borduas, P. Dubois, J. M. Chapuzet, T. H. Chan, J. Lessard, C. J. Li, *Chem. Eur. J.* **2010**, *16*, 8162-8166; b) M. Ferrari Bach, C. Herzer Griebeler, C. Gross Jacoby, P. H. Schneider, *Eur. J. Org. Chem.* **2017**, *2017*, 6997-7004; c) V. Gallo, P. Mastrorilli, C. F. Nobile, R. Paolillo, N. Taccardi, *Eur. J. Inorg. Chem.* **2005**, *2005*, 582-588.

[9] a) C. Chiappe, D. Capraro, V. Conte, D. Pieraccini, *Org. Lett.* **2001**, *3*, 1061-1063; b) C. Chiappe, E. Leandri, D. Pieraccini, *Chem. Commun.* **2004**, 2536-2537; c) P. Goodrich, H. Q. Nimal Gunaratne, L. Hall, Y. Wang, L. Jin, M. J. Muldoon, A. P. Ribeiro, A. J. Pombeiro, V. I.

Parvulescu, P. Davey, C. Hardacre, *Dalton Trans.* **2017**, *46*, 1704-1713; d) J. Li, S. Yang, H. Jiang, W. Wu, J. Zhao, *J. Org. Chem.* **2013**, *78*, 12477-12486; e) E. M. Omar, M. B. A. Rahman, B. Ni, A. D. Headley, *Synth. Commun.* **2019**, *49*, 1578-1591; f) Y. Qian, X. Zheng, Y. Wang, *Eur. J. Org. Chem.* **2010**, *2010*, 3672-3677; g) R. L. Vekariya, *Journal of Molecular Liquids* **2017**, *227*, 44-60; h) Z. Wang, Q. Wang, Y. Zhang, W. Bao, *Tetrahedron Letters* **2005**, *46*, 4657-4660; i) D. Wu, P. Cai, X. Zhao, Y. Pan, *Org. Lett.* **2017**, *19*, 5018-5021

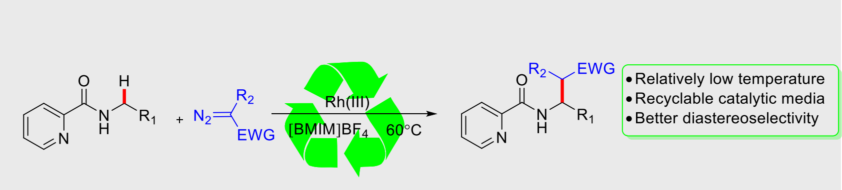
[10] a) J. M. Axten, R. Ivy, L. Krim, J. D. Winkler, *J. Am. Chem. Soc.* **1999**, *121*, 6511-6512; b) N. R. Candeias, P. M. Gois, C. A. Afonso, *J. Org. Chem.* **2006**, *71*, 5489-5497; c) H. M. Davies, Q. Jin, *Org Lett* **2004**, *6*, 1769-1772; d) H. M. Davies, A. Ni, *Chem. Commun.* **2006**, 3110-3112; e) H. M. Davies, C. Venkataramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* **2003**, *125*, 6462-6468; f) H. M. Davies, A. M. Walji, *Org. Lett.* **2003**, *5*, 479-482; g) H. M. L. Davies, T. Hansen, *J. Am. Chem. Soc.* **1997**, *119*, 9075-9076; h) H. M. L. Davies, T. Hansen, D. W. Hopper, S. A. Panaro, *J. Am. Chem. Soc.* **1999**, *121*, 6509-6510; i) M. P. Doyle, R. J. Pieters, J. Taunton, H. Q. Pho, A. Padwa, D. L. Hertzog, L. Precedo, *J. Org. Chem.***1991**, *56*, 820-829; j) D. M. Guptill, H. M. Davies, *J. Am. Chem. Soc.* **2014**, *136*, 17718-17721; k) Y. Nakagawa, S. Chanthamath, Y. Liang, K. Shibatomi, S. Iwasa, *J. Org. Chem.* **2019**, *84*, 2607-2618; l) D. Sole, A. Amenta, M. L. Bennasar, I. Fernandez, *Chem. Commun.* **2019**, *55*, 1160-1163; m) D. Sole, F. Mariani, M. L. Bennasar, I. Fernandez, *Angew. Chem.* 2016, 128, 6577 –6580; *Angew. Chem. Int. Ed.* **2016**, *55*, 6467-6470; m) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040-1052; n) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810-13889; o) X. Xiao, C. Hou, Z. Zhang, Z. Ke, J. Lan, H. Jiang, W. Zeng, *Angew. Chem*. **2016**, *128*, 12076 –12080; *Angew. Chem. Int. Ed.* **2016**, *55*, 11897-11901.

[11] H. Xie, Z. Ye, Z. Ke, J. Lan, H. Jiang, W. Zeng, *Chem. Sci.* **2018**, *9*, 985-989.

[12] J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506.

[13] a) J. Diesel, A. M. Finogenova, N. Cramer, *J Am Chem Soc* **2018**, *140*, 4489-4493; b) D. Katayev, E. Larionov, M. Nakanishi, C. Besnard, E. P. Kundig, *Chem. Eur. J.* **2014**, *20*, 15021-15030; c) D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.* **2012**, *3*, 3-14; d) J. H. Kim, S. Greßies, M. Boultadakis-Arapinis, C. Daniliuc, F. Glorius, *ACS Catal.* **2016**, *6*, 7652-7656; e) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kundig, *Angew. Chem. Int. Ed.* **2011**, *50*, 7438-7441; f) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kundig, *Chimia (Aarau)* **2012**, *66*, 241-243.

COMMUNICATION



[Cp*Rh^{III}] in an Ionic Liquid as a Highly Efficient and Recyclable Catalytic Medium for Regio-and Diastereoselective Csp^3-H Carbenoid Insertion

Csp3-H Carbenoid Insertion, Ionic Liquids

Jianglian Li, Lin Zhou, Yaoling Wang, Qiang Ma, Yuan Lei, Ruizhi Lai, Yi Luo, Li Hai and Yong Wu**

Page No.1 – Page No.5

[Cp*Rh^{III}] in an Ionic Liquid as a Highly Efficient and Recyclable Catalytic Medium for Regio-and Diastereoselective Csp^3-H Carbenoid Insertion