NRC Research Press

ARTICLE

Regioselective addition–elimination of Morita–Baylis–Hillman adducts with 2-naphthol or phenol catalyzed by functionalized ionic liquids: a direct strategy to construct functional alkenes

Chuan-Bao Zhang, Jun Zhang, Wei-Qiang Hu, Yan-Su Cui, Yong Liu, Ji-Ya Fu, and Tao Ding

Abstract: A highly regioselective addition–elimination of Morita–Baylis–Hillman adducts promoted by base ionic liquids (0.5 mol%) was reported to afford a variety of functional alkenes in excellent yields (up to 99%). This protocol provides a new method to access functional alkenes directly. Recycled base ionic liquids could be reused at least five times and the isolated yield of the product was almost consistent after five runs.

Key words: Morita–Baylis–Hillman adducts, functional ionic liquids, addition–elimination, regioselective.

Résumé : Nous faisons état d'une réaction d'addition–élimination hautement régiosélective menée sur des adduits de Morita–Baylis–Hillman, catalysée par des liquides ioniques (0,5 mol%) employés comme base et ayant produit une diversité d'alcènes fonctionnels dans d'excellents rendements (jusqu'à 99%). Le présent protocole offre une nouvelle méthode permettant d'accéder directement aux alcènes fonctionnels. En outre, les liquides ioniques employés comme bases recyclables peuvent être réutilisées au moins cinq fois; les rendements des produits isolés étant demeurés presque constants après cinq cycles. [Traduit par la Rédaction]

Mots-clés : adduits de Morita–Baylis–Hillman, liquides ioniques fonctionnels, addition–élimination, régiosélective.

Introduction

Functional alkene-containing compounds widely exist in natural products and pharmaceuticals of biological activities.[1] Regioselective addition–elimination of Morita–Baylis–Hillman (MBH) adducts is one of the most efficient methods for functional alkene formation, which are potentially important building blocks for a variety of valuable synthetic intermediates.[2] MBH carbonates as synthetically useful synthons have attracted significant attention from organic chemists.[3]

Over the past years, great progress has been made in the addition–elimination of MBH adducts. For the MBH adducts, the transformations of MBH carbonates have been directed toward the following two sites: substitution of MBH carbonates at the β- or β′-position with nucleophiles (Scheme 1).[4] Substitution of MBH carbonates at the β-position with nucleophiles has been well reported. [4] Substitution of MBH carbonates at the β′-position with nucleophiles has rarely been reported.[5] In 2006, P.V. Ramachandran developed a series of chiral phase-transfer catalysts for the direct substitution of MBH carbonates at the β′-position in excellent yields and high enantioselectivities.[5c] Subsequently, Y. Lu disclosed that quinidine-derived tertiary aminethiourea catalyst promoted the substitution of MBH carbonates at the β′-position with excellent yields and enantioselectivities.[5d] Even though, the direct substitution of MBH carbonates at the β′-position, especially 2-naphthol as nucleophile, is still a challenge.

Functionalized ionic liquids (FILs) are receiving growing attention in the fields of catalysis due to their unique structures, physical and chemical properties, and green credentials as reusable catalysts.[6] Recently, base ionic liquids (BILs) have emerged as an important type of functionalized ionic liquids and applied as resolution reagents, solvents, or catalysts.[7] Up to the present, numerous FILs have been designed and successfully applied in promoting various reactions.[8] However, to the best of our knowledge, no FIL catalysts have been used in the addition–elimination of MBH adducts, and it is still desirable to develop new efficient catalytic systems for this reaction.

Results and discussion

This work on the addition–elimination of MBH adducts with 2-naphthol showed that BILs were effective catalysts in this reaction. Inspired by this interesting result, herein, we wish to report our original work in the addition–elimination of MBH adducts with 2-naphthol catalyzed by BILs in excellent yields and regioselectivities (Chart 1).

For further investigation on this addition–elimination reaction, allylic carbonates (**1a**) and 2-naphthol (**2a**) were selected as model reactants and the results are summarized in Table 1. A variety of BIL catalysts **3a–3i** were synthesized and tested in the model reaction in CH_3CN at 40 °C (Table 1, entries 1–8), and the anions of the catalysts obviously affected the results. BIL catalysts **3e–3h** successfully gave **4a** in moderate yields (60%–85%) (Table 1, entries 5–8). Catalyst **3e** gave the best yield (85%) (Table 1, entry 5). To further optimize the reaction conditions, a series of solvents were investigated in the presence of 20 mol% **3e** and the results are presented in Table 1 (entries 10–17). All solvents gave moderate to good yields (57%–99%) except dichloromethane (DCM). When MeOH was used, 57% yield was obtained (Table 1, entry 12). Dimethyl sulfoxide (DMSO) delivered the highest yield (99%) at 40 °C (Table 1, entry 16). Based on these results, DMSO was chosen as a candidate solvent for further screenings (Table 1, entry 17).

Received 24 July 2015. Accepted 21 September 2015.

C.-B. Zhang, J. Zhang, W.-Q. Hu, Y.-S. Cui, Y. Liu, J.-Y. Fu, and T. Ding. College of Chemistry and Chemical Engineering, Henan University, Institute of Fine Chemistry and Engineering, Henan Engineering Laboratory of Flame-Retardant and Functional Materials, Kaifeng, Henan 475004, P. R. China.
Corresponding authors: Ji-Ya Fu (email: fujiya@126.com) and Tao Ding (email: dingtao@henu.edu.cn).

Can. J. Chem. **94**: 211–214 (2016) dx.doi.org/10.1139/cjc-2015-0358

Scheme 1. Substitution of MBH carbonates with pronucleophiles.

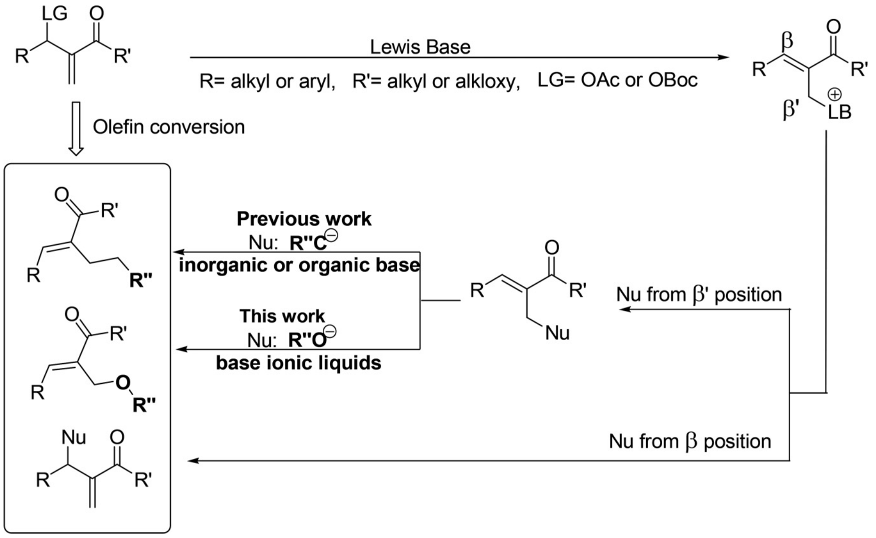
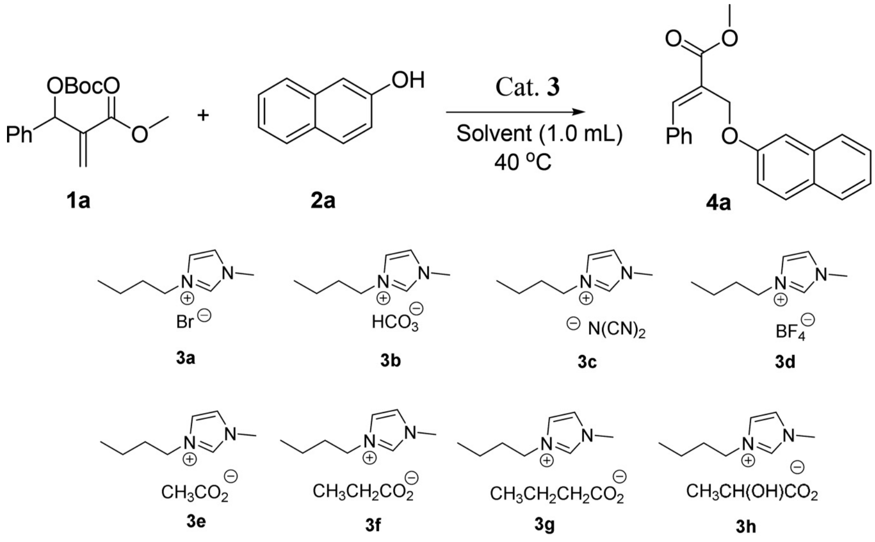


Chart 1. Reaction of allylic carbonates (**1a**) and 2-naphthol (**2a**).



To further improve the yields, other parameters such as catalyst loading, amount of MBH adducts, and temperature were also studied. The catalyst loading was also examined in DMSO at 40 °C and the results are described in Table 1 (entries 18–22). Catalyst loading exerted a slight influence on the yields. Lowering catalyst loading to 0.5 mol%, high yields were obtained (89%) (Table 1, entry 22). Further examinations showed that increasing the molar ratio of MBH adducts had no obvious change in yields (Table 1, entry 23). Decreasing the amount of MBH adducts significantly affected the yields (Table 1, entry 24). Continually, reaction temperature was studied. Lowering the temperature to 25 °C increased obviously the yields (98% yield) (Table 1, entry 25 versus 22). Thus, through those screenings, the optimized reaction conditions were found to be a reaction of 1.2 equiv. of **1a** with 1.0 equiv. of **2a** in the presence of 0.5 mol% of **3e** in DMSO at 25 °C (Table 1, entry 25).

Under optimized conditions, various MBH adducts (**1**) and 2-naphthol (**2a**) were evaluated (Chart 2) and the results are summarized in Table 2. Generally, all the cases proceeded smoothly and afforded the corresponding adducts **4** with moderate to excellent yields (59%–99%). Good results were obtained for different substituents on the phenyl of MBH adducts (Table 2, entries 1–14). Substituents on the 4-position of the phenyl group exerted obvious effects on the reactivities, and an obvious variety of yields were observed. Both electron-withdrawing and electron-donating substituents afforded lower yields (59%–73%) (Table 2, entries 3, 4, and 6–8) except 4-chlorophenyl-substituted MBH adducts (95%) (Table 2, entry 5). The position of the substituents was also tested. The yields were obviously sensitive to the position of the substituents on the aromatic of MBH adducts, although the para substituents gave higher yields compared with the corresponding meta- and ortho-substituted counterparts (Table 2, entries 5, 9 versus 13). 1-NaphthylMBH adducts gave an excellent yield (99%) (Table 2, entry 14). When the reaction was carried out on a multigram scale, a high yield was still obtained (92%) (Table 2, entry 2).

The addition–elimination of MBH adducts with phenol was also investigated (Table 2, entries 15–19). This catalytic system was still effective for phenol and 85%–99% yields were achieved. These results indicated that BIL **3e** was efficient for the addition–elimination of MBH adducts with 2-naphthol or phenol.

The reusability of ionic liquids is the key factor that identifies whether it finds a potential application in industry. To test the catalyst reusability and convenience of recycling, the reaction was

Table 1. Screening of catalysts and optimized conditions for the reaction of allylic carbonates (**1a**) and 2-naphthol (**2a**).

Entry	Catalyst	Solvent	Catalyst loading (%)	Time (h)	Yield (%)[a]
1	**3a**	CH_3CN	20	69	n.r.
2	**3b**	CH_3CN	20	69	n.r.
3	**3c**	CH_3CN	20	69	n.r.
4	**3d**	CH_3CN	20	69	n.r.
5	**3e**	CH_3CN	20	69	85
6	**3f**	CH_3CN	20	69	81
7	**3g**	CH_3CN	20	69	84
8	**3h**	CH_3CN	20	69	60
9	DABCO	CH_3CN	20	69	29
10	**3e**	DCM	20	192	Trace
11	**3e**	Et_2O	20	192	88
12	**3e**	MeOH	20	192	57
13	**3e**	EtOH	20	192	84
14	**3e**	THF	20	192	81
15	**3e**	DMF	20	3	83
16	**3e**	DMSO	20	2.5	99
17	**3e**	Toluene	20	192	Trace
18	**3e**	DMSO	10	4	97
19	**3e**	DMSO	5	4	96
20	**3e**	DMSO	2	5	96
21	**3e**	DMSO	1	15	94
22	**3e**	DMSO	0.5	15	89
23[b]	**3e**	DMSO	0.5	20	89
24[c]	**3e**	DMSO	0.5	20	73
25[d]	**3e**	DMSO	0.5	17	98

Note: Unless otherwise specified, all reactions were carried out with **1a** (0.18 mmol), **2a** (0.15 mmol), and catalyst **3** (20 mol%) in solvent (1.0 mL) at 40 °C.

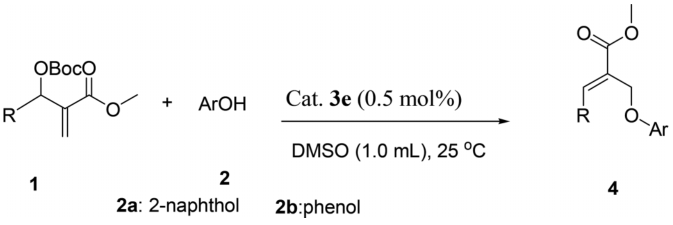
[a] Isolated yield; n.r., no reaction.

[b] Carried out by using 0.225 mmol of **1a** and 0.15 mmol of **2a**.

[c] Carried out by using 0.15 mmol of **1a** and 0.15 mmol of **2a**.

[d] Carried out at 25 °C.

Chart 2. Scope of substrates for the reaction of allylic carbonates (**1**) and 2-naphthol (**2**) under optimized conditions.



carried out in the presence of a catalytic amount of BIL **3e** under the conditions with **1i** (0.18 mmol), **2a** (0.15 mmol), and catalyst **3e** (20 mol%), and *t* = 24 h at 25 °C. When the reaction was completed, the reaction mixture was concentrated in vacuo and extracted with DCM and the ionic liquid left in the aqueous phase was concentrated in vacuo. Recycled BIL **3e** was directly used in the next run and the results indicated that the isolated yield of the product **4i** was almost consistent after five runs and **3e** could be reused at least five times (Fig. 1).

Conclusion

In summary, we have successfully demonstrated the regioselective addition–elimination of MBH adducts with 2-naphthol or phenol in excellent yields (up to 99%) efficiently promoted by environmental friendly FILs (0.5 mol%). This work provided an effective method for the construction of functional alkene compounds. Further applications of this transformation and new pharmaceutical preparations are currently underway in our laboratory.

Table 2. Scope of substrates.

Entry	R-group	2	Time (h)	Yield (%)[a]
1	Ph (**1a**)	**2a**	17	98 (**4a**)
2[b]	Ph (**1a**)	**2a**	20	92 (**4a**)
3	*p*-$NO_2C_6H_4$ (**1b**)	**2a**	138	59 (**4b**)
4	*p*-FC_6H_4 (**1c**)	**2a**	23	68 (**4c**)
5	*p*-ClC_6H_4 (**1d**)	**2a**	45	95 (**4d**)
6	*p*-BrC_6H_4 (**1e**)	**2a**	23	73 (**4e**)
7	*p*-$CH_3C_6H_4$ (**1f**)	**2a**	138	71 (**4f**)
8	*p*-$CH_3OC_6H_4$ (**1g**)	**2a**	52	67 (**4g**)
9	*o*-ClC_6H_4 (**1h**)	**2a**	138	83 (**4h**)
10	*o*-BrC_6H_4 (**1i**)	**2a**	23	69 (**4i**)
11[c]	*o*-BrC_6H_4 (**1i**)	**2a**	24	88 (**4i**)
12	*o*-$CH_3C_6H_4$ (**1j**)	**2a**	138	99 (**4j**)
13	*m*-ClC_6H_4 (**1k**)	**2a**	137	90 (**4k**)
14	1-naphthyl (**1l**)	**2a**	23	99 (**4l**)
15	**1a**	**2b**	6	89 (**4m**)
16	**1f**	**2b**	18	90 (**4n**)
17	**1i**	**2b**	1	85 (**4o**)
18	**1j**	**2b**	1	93 (**4p**)
19	**1l**	**2b**	18	99 (**4q**)

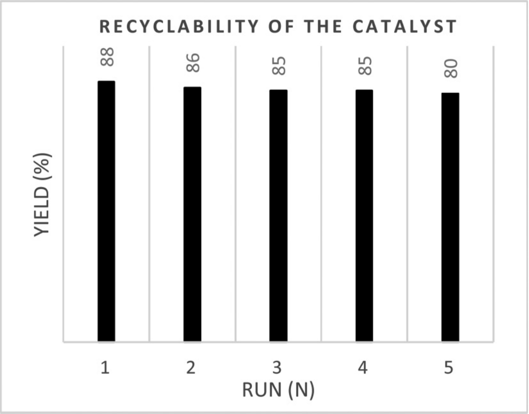
Note: Unless otherwise specified, all reactions were carried out with **1** (0.18 mmol), **2a** (0.15 mmol), and catalyst **3e** (0.5 mol%) in DMSO (1.0 mL) at 25 °C.

[a] Isolated yield.

[b] Carried out with **1a** (4.5 mmol), **2a** (3.75 mmol), and catalyst **3e** (0.5 mol%) in DMSO (25 mL) at 25 °C.

[c] Carried out with **1i** (0.18 mmol), **2a** (0.15 mmol), and catalyst **3e** (20 mol%) in DMSO (1.0 mL) at 25 °C.

Fig. 1. Recyclability of the catalyst. Reaction conditions: **1i** (0.18 mmol), **2a** (0.15 mmol), catalyst **3e** (20 mol%), *t* = 24 h, 25 °C.



Supplementary material

Supplementary material is available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2015-0358.

Acknowledgements

This work was supported by the Science and Technology Development Project of Henan Province (No. 134300510072) and the National Natural Science Foundation of China (No. 21206031).

References

(1) (a) Shanmugam, P.; Vaithiyanathan, V. *Tetrahedron* **2008**, *64*, 3322. doi:10.1016/j.tet.2008.02.002; (b) Zhang, P. Z.; Gu, J.; Zhang, G. L. *J. Asian Nat. Prod. Res.* **2015**, *17*, 217. doi:10.1080/10286020.2015.1006202; (c) Hikosaka, G.; Hattori, Y.; Makabe, H. *Tetrahedron* **2014**, *25*, 1367. doi:10.1016/j.tetasy.2014.08.008.

(2) Selected examples: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. doi:10.1021/cr010043d; (b) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. doi:10.1021/cr068057c; (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. doi:10.1016/j.tet.2008.02.087; (d) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614. doi:10.1002/anie.

200604366; (e) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905. doi:10.1002/ejoc.200700030; (f) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496. doi:10.1039/b909405a.

(3) Selected example: Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348. doi:10.1021/ol201094f.

(4) Selected examples: (a) Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. *Org. Lett.* **2011**, *13*, 3972. doi:10.1021/ol201490e; (b) Deng, H.-P.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 1956. doi:10.1002/ejoc.201001660; (c) Pei, C.-K.; Zhang, X.-C.; Shi, M. *Eur. J. Org. Chem.* **2011**, 4479. doi:10.1002/ejoc.201100501; (d) Yang, W.; Wei, X.; Pan, Y.; Lee, R.; Zhu, B.; Liu, H.; Yan, L.; Huang, K.-W.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2011**, *17*, 8066. doi:10.1002/chem.201100929; (e) Hon, L.; Sun, W.; Liu, C.; Zhao, D.; Wang, R. *Chem. Commun.* **2010**, *46*, 2856. doi:10.1039/b926037d; (f) Huang, J.-R.; Cui, H.-L.; Lei, J.; Sun, X.-H.; Chen, Y.-C. *Chem. Commun.* **2011**, *47*, 4784. doi:10.1039/C0CC05616B; (g) Yang, Y.-L.; Pei, C.-K.; Shi, M. *Org. Biomol. Chem.* **2011**, *9*, 3349. doi:10.1039/C1OB00017A; (h) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. doi:10.1021/ja802422d; (i) Kamlar, M.; Hybelbauerová, S.; Císařová, I.; Veselý, J. *Org. Biomol. Chem.* **2014**, *12*, 5071. doi:10.1039/c4ob00682h; (j) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 3914. doi:10.1021/ol101601d; (k) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101. doi:10.1039/c2cs35017c.

(5) Selected examples: (a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534. doi:10.1021/ja994326n; (b) Roy, S. J. S.; Mukherjee, S. *Chem. Commun.* **2014**, *50*, 121. doi:10.1039/C3CC47645F; (c) Ramachandran, P. V.; Madhi, S.; Bland-Berry, L.; Reddy, M. V. R.; O'Donnel, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450. doi:10.1021/ja052638m; (d) Chen, G.-Y.; Zhong, F.; Lu, Y. *Org. Lett.* **2011**, *13*, 6070. doi:10.1021/ol202555v; (e) Badkar, P. A; Rath, N. P.; Spilling, C. D. *Org. Lett.* **2007**, *9*, 3619. doi:10.1021/ol701500s; (f) Chen, C.-G.; Hou, X.-L.; Pu, L. *Org. Lett.* **2009**, *11*, 2073. doi:10.1021/ol900439h.

(6) Selected examples: (a) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772. doi:10.1002/1521-3773(20001103)39:21<3772::AID-ANIE3772>3.0.CO;2-5; (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. doi:10.1021/cr980032t; (c) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73. doi:10.1039/b110838g.

(7) Selected examples: (a) Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2005**, *70*, 2338. doi:10.1021/jo048391d; (b) Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049. doi:10.1002/1521-3773(20000901)39:17<3049::AID-ANIE3049>3.0.CO;2-5; (c) Mi, X. L.; Luo, S. Z.; He, J. Q.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4567. doi:10.1016/j.tetlet.2004.04.039; (d) Sheldon, R. *Chem. Commun.* **2001**, 2399. doi:10.1039/b107270f.

(8) Selected examples: (a) Rosa, J. N.; Afonso, C. A. M.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4189. doi:10.1016/S0040-4020(01)00316-7; (b) Hsu, J.-C.; Yen, Y.-H.; Chu, Y.-H. B. *Tetrahedron Lett.* **2004**, *45*, 4673. doi:10.1016/j.tetlet.2004.04.099; (c) Kim, E. J.; Ko, S. Y. *Helv. Chim. Acta* **2003**, *86*, 894. doi:10.1002/hlca.200390087.