Letter

Synthesis of 2-Benzazepines from Benzylamines and MBH Adducts Under Rhodium(III) Catalysis via C(sp2)–H Functionalization

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Synthesis of 2-Benzazepines from Benzylamines and MBH Adducts Under Rhodium(III) Catalysis via C(sp^2)–H Functionalization

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ABSTRACT: The rhodium(III)-catalyzed cross-coupling reaction between commercially available benzylamines and Morita–Baylis–Hillman (MBH) adducts is described. This protocol provides a facile access to various 2-benzazepine derivatives via the C(sp^2)–H activation of *N*-allylated benzylamines and subsequent intramolecular olefin insertion followed by *N*-allylation reaction. A range of substrates has been used and a high level of chemoselectivity as well as functional group tolerance was observed. To gain mechanistic insight of this transformation, DFT calculations were also performed.

KEYWORDS: benzazepines, benzylamines, C–H activation, Morita–Baylis–Hillman adducts, rhodium.

Azepine analogues are among the most interesting discovery in the field of natural products and pharmaceuticals. Particularly, benzazepine derivatives have attracted considerable attention by virtue of their interesting biological properties.[1] Typical examples, such as galanthamine, capsazepine (CPZ), and baclabuvir include the 2-benzazepine scaffold (Figure 1).[2] Consequently, the synthesis of 2-benzazepines is of great interest in organic and medicinal chemistry.

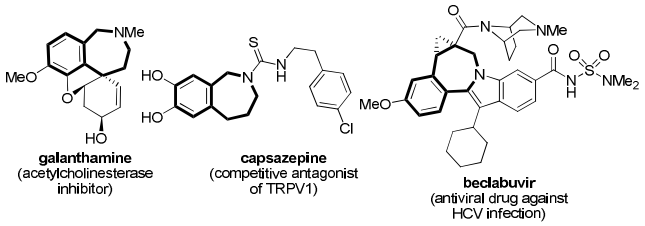


Figure 1. Selected examples with 2-benzazepine scaffold

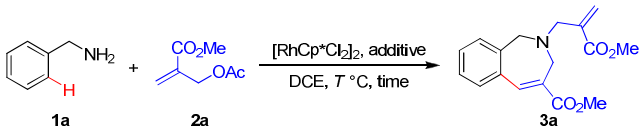
Transition-metal-catalyzed C–H functionalization has been one of the most attractive issues in organic synthesis due to its remarkable potential for step economy and environmental sustainability.[3] Recently, much attention has been made towards the C(sp^2)–H functionalization of protected or unprotected benzylamines affording *N*-containing heterocycles. For example, Orito described the C–H activation of *N*-alkyl benzylamines followed by subsequent carbonylation process for the preparation of benzolactams.[4a] Kim reported the direct access to isoindolines through Rh(III)-catalyzed alkenylation and cyclization of *N*-benzyltriflamides.[4b] In addition, Miura beautifully demonstrated the Ru(II)- and Rh(III)-catalyzed dehydrogenative *ortho*-alkenylation and annulation of unprotected benzylamines with acrylates.[4c] In the same time, Ariza and Garcia have also used unprotected benzylamines to be coupled with allenes providing tetrahydroisoquinolines under Pd(II) catalysis.[4d]

The Morita–Baylis–Hillman (MBH) reaction has been recognized as a useful carbon-carbon bond-forming reaction for organic chemists.[5] In particular, MBH adducts are useful precursors for the preparation of substituted alkenes including bioactive molecules by the reaction of a wide range of coupling partners.[6] In this context, Kim developed the facile synthesis of polycyclic compounds using haloaryl-containing MBH acetates and *N*-heterocyclic nucleophiles.[7] Alper disclosed the synthesis of azepinones through Pd(II)-catalyzed amination and intramolecular cyclocarbonylation reactions of primary amines and MBH adducts.[8] Very recently, Ding has utilized the racemic Morita–Baylis–Hillman adducts to generate asymmetric allylic allylated products with allylB(pin) under palladium catalysis.[9] In continuation of our recent studies on the synthesis of biologically relevant heterocyclic molecules based on catalytic C–H functionalization,[10] we herein first present the Rh(III)-catalyzed synthesis of 2-benzazepines from benzylamines using Morita–Baylis–Hillman adducts via the *N*-allylation of primary benzylamines followed by intramolecular olefin insertion process.

Our study was initiated by investigating the coupling reaction of benzylamine (**1a**) and methyl 2-(acetoxymethyl)acrylate (**2a**), as shown in Table 1. We were delighted to see the coupling reaction between **1a** and **2a** under cationic Rh(III) catal-

ysis in DCE at 60 °C providing the desired product **3a** in 40% yield (Table 1, entry 1). Control experiments revealed that cationic rhodium catalyst is highly crucial for this transformation (Table 1, entry 2). The use of $Cu(OAc)_2$ as an acetate source was found to be efficient in this coupling reaction (Table 1, entries 3–6). In this stage, other transition-metal catalysts such as Ru(II), Co(III) and Ir(III) were screened, and Rh(III) was found to be a most effective catalyst (See Supporting Information for details). In addition, decreasing amount of $Cu(OAc)_2$ to 70 mol % enhanced the formation of **3a** up to 65% yield (Table 1, entries 7 and 8). However, the shorten reaction time at 60 °C was found to be less effective (Table 1, entry 9). Increasing the temperature to 110 °C for 10 min led to the formation of **3a** in high yield (72%) (Table 1, entries 10–12). Screening of solvents indicated that DCE is an optimal solvent for the preparation of **3a** (See Supporting Information for details). Exchanging silver additives to $AgNTf_2$ and $AgPF_6$ gave 60% and 25% yields of **3a**, respectively (Table 1, entries 13 and 14). A preformed cationic Rh(III) complex was also found to be comparable in this reaction (Table 1, entry 15). Finally, this transformation can be readily scaled up to 1.07 mmol to give **3a** in 61% yield (Table 1, entry 16).

Table 1. Optimization for Reaction Conditions[a]



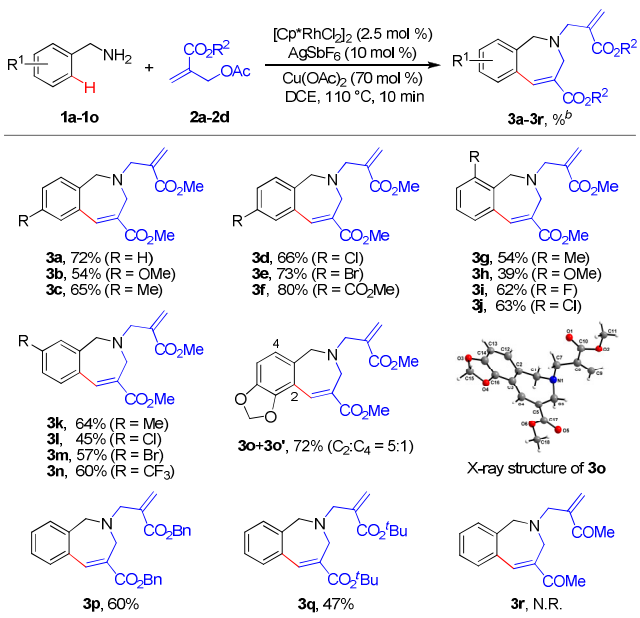
1a **2a** **3a**

entry	additive (mol %)	T °C	time	yield[b]
1	$AgSbF_6$ (10)	60	18 h	40
2		60	18 h	N.R.
3	$AgSbF_6$ (10), $Cu(OAc)_2$ (100)	60	18 h	59
4	$AgSbF_6$ (10), CuOAc (100)	60	18 h	55
5	$AgSbF_6$ (10), NaOAc (100)	60	18 h	18
6	$AgSbF_6$ (10), KOAc (100)	60	18 h	15
7	$AgSbF_6$ (10), $Cu(OAc)_2$ (70)	60	18 h	65
8	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	60	18 h	61
9	$AgSbF_6$ (10), $Cu(OAc)_2$ (70)	60	2 h	35
10	$AgSbF_6$ (10), $Cu(OAc)_2$ (70)	80	2 h	53
11	$AgSbF_6$ (10), $Cu(OAc)_2$ (70)	110	30 min	58
12	**$AgSbF_6$ (10), $Cu(OAc)_2$ (70)**	**110**	**10 min**	**72**
13	$AgNTf_2$ (10), $Cu(OAc)_2$ (70)	110	10 min	60
14	$AgPF_6$ (10), $Cu(OAc)_2$ (70)	110	10 min	25
15[c]	$Cu(OAc)_2$ (70)	110	10 min	68
16[d]	$AgSbF_6$ (10), $Cu(OAc)_2$ (70)	110	10 min	61

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (quantity noted), DCE (1 mL) under air at indicated temperature in pressure tubes. [b] Isolated percent yield by flash column chromatography. [c] A preformed $[RhCp^*(MeCN)_3(SbF_6)_2]$ (5 mol %) complex was used as a catalyst. [d] Scale-up experiment: **1a** (1 g, 1.07 mmol) was used.

With the optimized reaction conditions in hand, the substrate scope and limitation of this reaction were examined, as shown in Table 2. The reaction of *para*-substituted benzylamines **1b**–**1f** with both electron-donating and electron-withdrawing groups was found to be good substrates in this transformation affording the corresponding products **3b**–**3f** in good to high yields under the present reaction conditions. The reaction conditions are tolerant to bromo and ester functional groups, therefore furnishing a versatile synthetic elaboration. We were delighted to see that *ortho*- and *meta*-substituted benzylamines **1g**–**1n** were also compatible to afford our desired products **3g**–**3n** in moderate to good yields. Interestingly, piperonylamine **1o** was coupled with **2a** giving a mixture of 2-benzazepines **3o** and **3o'**, which were derived from the reaction on C_2–H and C_4–H, with 5:1 ratio in 72% combined yields. Further isolation of **3o** was undertaken, and the structure of **3o** was confirmed by the X-ray crystallographic analysis. After screening the scope of benzylamines, we further evaluated the scope of MBH adducts under the optimal reaction conditions. MBH adducts **2b** and **2c**, generated from benzyl and *tert*-butyl acrylates using paraformaldehyde, were subjected to react with benzylamine (**1a**) to deliver our desired products **3p** and **3q** in 60% and 47% yields, respectively. However, MBH reagent **2d** derived from methyl vinyl ketone did not undergo the coupling reaction to provide the corresponding 2-benzazepine **3r**.

Table 2. Scope of Benzylamines and MBH Adducts[a]

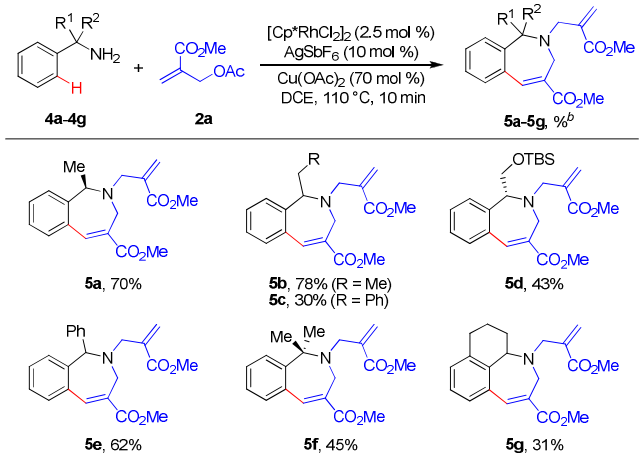


[a] Reaction conditions: **1a**–**1o** (0.2 mmol), **2a**–**2d** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (70 mol %), DCE (1 mL) under air at 110 °C for 10 min in pressure tubes. [b] Isolated yield by flash column chromatography.

Next, the scope of α-substituted benzylamines **4a**–**4g** was explored with **2a**, as shown in Table 3. 1-Phenylethanamine (**4a**) and α-ethyl substituted benzylamine **4b** were successfully reacted with **2a** providing **5a** (70%) and **5b** (78%), respectively. However, α-benzyl substituted benzylamine **4c** was found to be relatively less reactive for the formation of **5c**. Notably, this reaction readily proceeded with benzylamine **4d**, which was derived from its corresponding phenylglycine, furnishing **5d** in 43 % yield. It should be mentioned that no racemization of chiral substrates **4a** and **4d** was observed under the current reaction conditions. In addition, benzhydrylamine (**4e**) was

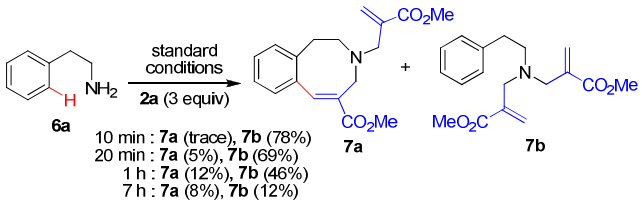
found to be a good substrate in this transformation. To our pleasure, sterically congested benzylamine **4f** and tetrahydro-1-naphthylamine **4g** were also favored in the coupling reaction to afford the corresponding 2-benzazepine **5f** and tricyclic azepine **5g**, respectively.

Table 3. Scope of α-Substituted Benzylamines[a]



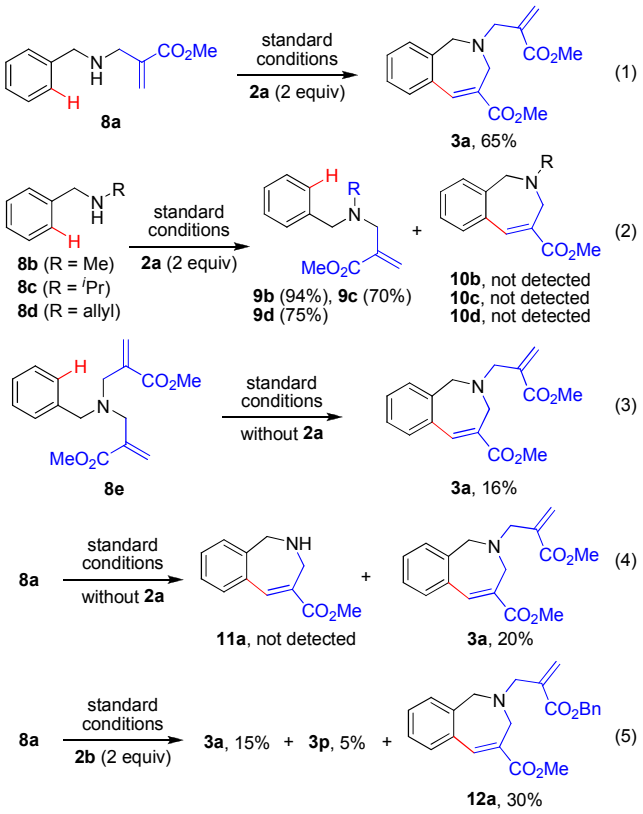
[a] Reaction conditions: **4a**–**4g** (0.2 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (70 mol %), DCE (1 mL) under air at 110 °C for 10 min in pressure tubes. [b] Isolated yield by flash column chromatography.

With the results for the formation of 2-benzazepines from benzylamines, we have been interested in the synthesis of 8-membered azocine using 2-phenethylamine **6a** with **2a** (Scheme 1). Under the standard reaction conditions for 10 min, a trace amount of azocine **7a** was observed, and *N*,*N*'-diallylated tertiary phenethylamine **7b** was formed in 78% yield. To investigate the effect of reaction time, we performed a series of reaction with increased reaction times, but the yield of **7a** could not be improved.



Scheme 1. Synthesis of 8-Membered Azocine

To recognize the formation of 2-benzazepines in this process, various control experiments were subjected, as shown in Scheme 2. Firstly, treatment of **8a** with **2a** provided our desired product **3a** in 65% yield (Scheme 2, eq. 1). However, secondary benzylamines **8b**–**8d** were coupled with **2a** to furnish *N*-allylated compounds **9b**–**9d** in good yields, and no formation of 2-benzazepine adducts **10b**–**10d** was detected (Scheme 2, eq. 2). Based on the result for the reaction of *N*-allylated benzylamine **8d** with **2a**, we suggest that *N*-allylated secondary benzylamine **8a** containing an ester functionality on the vinylic position is highly desirable intermediate for the formation of 2-benzazepine. This result can be rationalized by the theoretical study between **8a** and **8d** (see Figure S1 in Supporting Information for details). To further confirm whether *N*,*N*'-diallylated tertiary benzylamine **8e** is a crucial intermediate in this process, we performed the intramolecular cyclization reaction of **8e** in the absence of **2a** (Scheme 2, eq. 3). Interestingly, the formation of **3a** was observed in 16% yield. This observation can be explained by the deallylation of **8e** to afford secondary benzylamine **8a**, which can undergo the C(sp^2)–H activation and subsequent intramolecular olefin insertion followed by *N*-allylation reaction. The deallylation reaction can be further confirmed by the reaction of **8a** in the absence of **2a** under the standard reaction conditions, resulting in the formation of **3a** in 20% yield (Scheme 2, eq. 4). Unfortunately, free-(NH)-2-benzazepine **11a** could not be detected presumably due to the rapid *N*-allylation reaction of **11a** with **8a** as an internal allyl source. Finally, the cross-over experiment of **8a** with **2b** suggests that this transformation proved to be competitive between deallylation and intramolecular cyclization of secondary *N*-allylated intermediates (Scheme 2, eq. 5).



Scheme 2. Mechanistic Investigation

Based on the above mechanistic investigation and preceding literatures on the Rh(III)-catalyzed alkenylation reactions using olefins,[11] a plausible reaction mechanism is outlined in Scheme 3. Initially, benzylamine (**1a**) reacts with MBH adduct **2a** through the S_N2' pathway to afford secondary benzylamine **8a**, which can undergo C–H activation process with a cationic Rh(III) species, generating a rhodacycle intermediate **I**. Subsequently, olefin coordination and migratory insertion take place to give seven-membered Rh(III) complex **II**, which undergoes β-H–elimination to deliver the intermediate **11a** and Rh(III) catalyst. Finally, the *N*-allylation of **11a** can furnish our desired product **3a**.

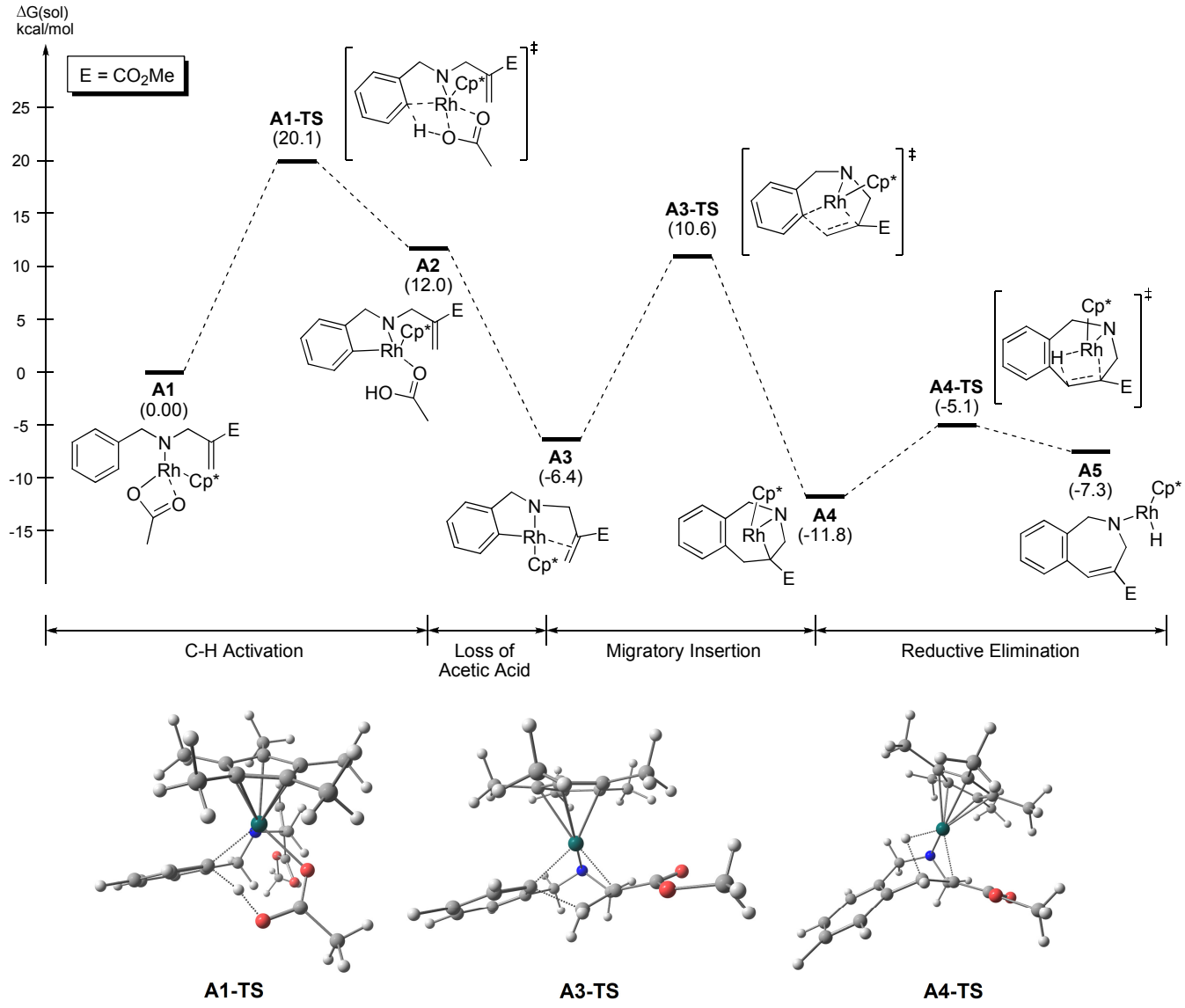
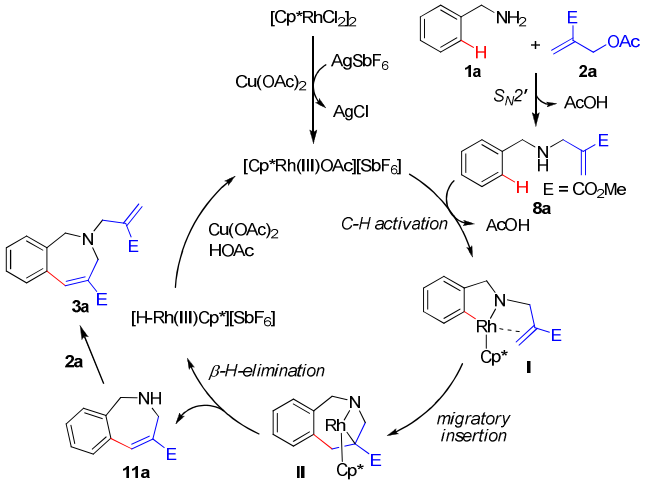


Figure 2. Energy profiles of proposed reaction mechanism



Scheme 3. Plausible Reaction Mechanism

To gain more insight into the reaction mechanism, DFT calculations were performed with the B3LYP[12] and M06[13] hybrid functional to get a detailed overview of Gibbs free energy at 383.15 K (See the Supporting Information for computational details). The intermediate **A1** undergoes C–H bond activation via **A1-TS**, in which the acetate ligand deprotonates an *ortho* proton to afford the transient intermediate **A2** at a relative energy of 12.0 kcal/mol (Figure 2). This concerted metalation-deprotonation (CMD) step is the most energy demanding with a kinetic barrier of 20.1 kcal/mol, which suggests that the rate determining step should be the CMD reaction. Consecutively, the 5-membered rhodacycle **A2** loses AcOH, providing a vacant binding site on Rh(III) for the olefin coordination. The resulting intermediate **A3** is located at -6.4 kcal/mol and ready for migratory insertion. In the most favorable pathway, our computed transition state structures illustrate that the rhodacycle **A3** adds to the endo face of the olefin,[14] and the

transition state for the migratory insertion step **A3-TS** is located at 10.6 kcal/mol with a barrier of 17.0 kcal/mol, forming seven-membered Rh(III) complex **A4** (located at -11.8 kcal/mol). Next, **A4** undergoes β-H–elimination to deliver the intermediate **A5** with a small barrier of 6.7 kcal/mol.

In conclusion, we described the first rhodium(III)-catalyzed cross-coupling reaction between benzylamines and Morita–Baylis–Hillman (MBH) adducts to afford a variety of 2-benzazepine derivatives. This protocol has been applied to a wide range of substrates, and typically proceeds with excellent levels of chemoselectivity as well as with high functional group tolerance. Additionally, the reaction pathway of this process was recognized by experimental and theoretical investigations. The biological evaluation of synthetic 2-benzazepines is underway and will be reported in due course.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information

The detailed optimization results, experimental procedures, characterization data, chiral HPLC analysis of **5a** and **5d**, DFT calculation details, X-ray crystallographic data of **3o**, and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

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REFERENCES

(1) (a) Ellis, G. P.; West, G. B. *Progress in Medicinal Chemistry*; Elsevier: Oxford, 1990, vol. 27, pp 123–141. (b) Katritzky, A. R.; Boulton, A. J. *Advances in Heterocyclic Chemistry*, Elsevier: New York, 1974, vol. 17, pp 45–98. (c) Kawase, M.; Saito, S.; Motohashi, N. *Int. J. Antimicrob. Agents* **2000**, *14*, 193–201. (d) So, M.; Kotake, T.; Matsuura, K.; Inui, M.; Kamimura, A. *J. Org. Chem.* **2012**, *77*, 4017–4028.

(2) (a) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123,* 6740–6741. (b) Walpole, C. S.; Bevan, S.; Bovermann, G.; Boelsterli, J.; Breckenridge, R.; Davies, J. W.; Hughes, G. A.; James, I.; Oberer, L. *J. Med. Chem.* **1994**, *37*, 1942–1954. (c) Berglund, M.; Dalence-Guzman, M. F.; Skogvall, S.; Sterner, O. *Bioorg. Med. Chem.* **2008**, *16*, 2529–2540. (d) Gentles, R. G.; Ding, M.; Bender, J. A.; Bergstrom, C. P.; Grant-Young, K.; Hewawasam, P.; Hudyma, T.; Martin, S.; Nickel, A.; Regueiro-Ren, A.; Tu, Y.; Yang, Z.; Yeung, K.-S.; Zheng, X.; Chao, S.; Sun, J.-H.; Beno, B. R.; Camac, D. M.; Chang, C.-H.; Gao, M.; Morin, P. E.; Sheriff, S.; Tredup, J.; Wan, J.; Witmer, M. R.; Xie, D.; Hanumegowda, U.; Knipe, J.; Mosure, K.; Santone, K. S.; Parker, D. D.; Zhuo, X.; Lemm, J.; Liu, M.; Pelosi, L.; Rigat, K.; Voss, S.; Wang, Y.; Wang, Y.-K.; Colonno, R. J.; Gao, M.; Roberts, S. B.; Gao, Q.; Ng, A.; Meanwell, N. A.; Kadow, J. F. *J. Med. Chem.* **2014**, *57*, 1855–1879.

(3) For recent reviews, see: (a) Mishra, N. K.; Sharma, S.; Park, J.; Han, S.; Kim, I. S. *ACS Catal.* **2017**, *7*, 2821–2847. (b) Wang, F.; Yu, S.; Li, X. *Chem. Rev.* **2016**, *45*, 6462–6477. (c) Li, S.-S.; Qin, L.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 4554–4570. (d) Rao, W.-H.; Shi, B.-F. *Org. Chem. Front.* **2016**, *3*, 1028–1047. (e) Sharma, S.; Mishra, N. K.; Shin, Y.; Kim, I. S. *Curr. Org. Chem.* **2016**, *20*, 471–511.

(4) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342–14343. (b) Mishra, N. K.; Park, J.; Sharma, S.; Han, S.; Kim, M.; Shin, Y.; Jang, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2014**, *50*, 2350–2352. (c) Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2014**, *356*, 1521–1526. (d) Rodríguez, A.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J.; Farràs, J.; Mela, A. L.; Nicolás, E. *J. Org. Chem.* **2014**, *79*, 9578–9585.

(5) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670.

(6) For selected examples, see: (a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659–6690. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892. (c) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803–3805. (d) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101–4112. (e) Bhowmic, S.; Batra, S. *Curr. Org. Chem.* **2014**, *18*, 3078–3119.

(7) (a) Kim, J. N.; Im, Y. J.; Gong, J. H.; Lee, K. Y. *Tetrahedron Lett.* **2001**, *42*, 4195–4197. (b) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343–345. (c) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613–2616. (d) Lee, H. J.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **1999**, *40*, 4363–4367.

(8) Cao, H.; Vieira, T. O.; Alper, H. *Org. Lett.* **2011**, *13*, 11–13.

(9) Wang, X.; Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 1116–1119.

(10) (a) Sharma, S.; Han, S. H.; Han, S.; Ji, W.; Oh, J.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2015**, *17*, 2852–2855. (b) Mishra, N. K.; Choi, M.; Jo, H.; Oh, Y.; Sharma, S.; Han, S. H.; Jeong, T.; Han, S.; Lee, S.-Y.; Kim, I. S. *Chem. Commun.* **2015**, *51*, 17229–17232. (c) Jeong, T.; Han, S. H.; Han, S.; Sharma, S.; Park, J.; Lee, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2016**, *18*, 232–235. (d) Han, S. H.; Mishra, N. K.; Jo, H.; Oh, Y.; Jeon, M.; Kim, S.; Kim, W. J.; Lee, J. S.; Kim, H. S.; Kim, I. S. *Adv. Synth. Catal.* **2017**, *359*, 2396–2401.

(11) (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407–1409. (b) Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5430–5433. (c) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983. (d) Li, B.; Ma, J.; Xie, W.; Song, H.; Xu, S.; Wang, B. *Chem. Eur. J.* **2013**, *19*, 11863–11868. (e) Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5393–5397.

(12) (a) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200–206. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(13) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(14) The barrier for exo addition to olefin is prohibitively large (7.0 kcal/mol relative to **A3-TS**).

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