Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

A Rapid Synthesis of Chiral Allylic Amines via Microwave-assisted Asymmetric Alkenylation of *N*-Tosyl Aldimines Catalyzed by Rhodium/Chiral Diene Complexes

Balraj Gopula,[a] Hao-Wei Zeng,[a] Ping-Yu Wu,[b] Julian P. Henschke[b] and Hsyueh-Liang Wu[a]*

[a]*Department of Chemistry, National Taiwan Normal University, Taiwan, Republic of China*
[b]*ScinoPharm, Taiwan Science-Based Industrial Park, Taiwan, Republic of China*

(Received: December 29, 2016; Accepted: March 9, 2017; DOI: 10.1002/jccs.201600888)

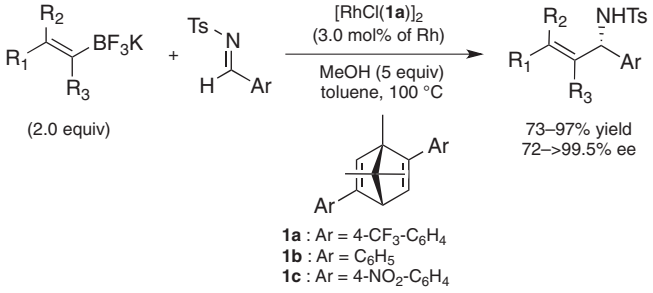
A method providing expeditious access to chiral allylic amines via a Rh(I)/bicyclo[2.2.1]heptadiene-catalyzed enantioselective alkenylation of *N*-tosyl aldimines with potassium alkenyltrifluoroborates under microwave irradiation is described. The rate of the asymmetric 1,2-addition reaction, conducted in the presence of 1 mol % of the catalyst, was significantly enhanced as compared to when the standard heating method was applied while still providing the corresponding products without decrease in enantioselectivity.

Keywords: Microwave irradiation; Chiral allylic amine; Enantioselective.

INTRODUCTION

Optically active amines are prevalent in natural and synthetic molecules with biological and pharmacological activity. Consequently, the development of efficient synthetic methods for their preparation has been an important part of synthetic organic chemistry.[1] In particular, the synthesis of chiral allylic amines has attracted considerable attention because of the widespread existence of this moiety in compounds of interest and because of the synthetic versatility of the olefinic group.[2] Pd- or Ir-catalyzed enantioselective substitution reactions of amino nucleophiles with allylic electrophiles have often been employed to produce optically active allylic amines.[3] Further, rearrangement of allylic imidates in the presence of Pd catalysts proceed in a highly enantioselective manner to furnish allylic amines.[4] While chiral allylic amines can be synthesized by a number of other useful methods[5] including the enantioselective addition of alkenylboronic acids to *in situ* generated iminium salts or imines catalyzed by organocatalysts, known as the asymmetric Petasis reaction,[6] the Rh(I)-catalyzed diastereoselective alkenylation reaction of chiral *N*-*tert*-butanesulfimines with alkenylboronic nucleophilic donors has emerged as a preferred approach to chiral allylic amines.[7] Although operating in a highly selective manner, the chirality-inducing *N*-*tert*-butanesulfinyl moiety must be employed in a stoichiometric amount. Subsequent to this, the asymmetric Rh(I)-catalyzed 1,2-addition of potassium aryl or alkenyltrifluoroborates without recourse to a chiral auxiliary was reported, but only *N*-sulfonylketimines[8,9] and benzoxathiazine-2,2-dioxides[9] were reported as substrates. Recently, we reported the first example of the catalytic asymmetric 1,2-addition of potassium alkenyltrifluoroborates to simple *N*-tosyl aryl aldimines, derived from tosyl amide and arylaldehydes.[10] Rh(I) catalysts comprising chiral bicyclo[2.2.1] heptadiene ligands **1** have often proved to be highly enantioselective in this transformation (Scheme 1). Despite the high selectivity and versatility of this method, extended reaction times were generally required to effect full conversion even though the reaction was conducted at 100 °C. The use of microwave irradiation[11] in transition-metal-catalyzed reactions has enabled very short reaction times while not causing any loss of stereoselectivity as compared to the thermal version of the reactions.[12,13] More recently, we have achieved the microwave-assisted 1,4-conjugate addition reaction of alkenylboronic acids to a cyclopentenone for the synthesis of prostaglandins.[14] Based on this and our previously established results, the enantioselective alkenylation of *N*-tosyl aryl and heteroaryl aldimines catalyzed by rhodium/chiral diene catalysts under microwave irradiation is reported here.

*Corresponding author. E-mail: hlw@ntnu.edu.tw

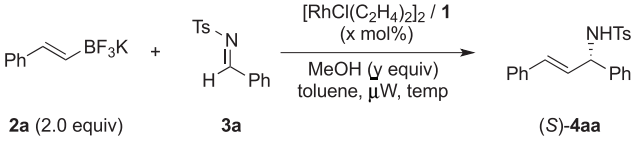


Scheme 1. Enantioselective alkenylation under thermal reaction conditions.

RESULTS AND DISCUSSION

Initially, to confirm that the Rh(I)/chiral diene catalysts functioned in the microwave-irradiated reaction as in the thermal counterpart, the optimal reaction parameters obtained from the thermally heated reactions were adopted (Table 1).[10] The addition of potassium styryltrifluoroborate (**2a**) to benzaldimine (**3a**), in the presence of 1.5 mol % of the preformed [RhCl(**1a**)]$_2$ complex, was carried out under microwave irradiation at 100°C, exclusively providing (*E*)-**4aa** in 70% yield and 93% ee after 1 h (entry 1). Although much more rapid, the yield was inferior as compared to that of the thermal version of the reaction (92%).[10] A very similar result was obtained under microwave irradiation after 3 h when conducted in the presence of 3 mol % of the Rh(I)/**1a** catalyst generated *in situ* from 1.5 mol % of [RhCl(C_2H_4)$_2$]$_2$ and chiral diene **1a** (entry 2). While the addition product was obtained in only 35% yield and 94% ee using the catalyst comprising diene ligand **1b** (entry 3), the reaction carried out in the presence of the Rh(I)/**1c** catalyst afforded allylic *N*-Ts-amine **4aa** in 72% yield with 95% ee (entry 4). When employing the Rh(I)/**1c** catalyst at 200 °C, product **4aa** was isolated in 94% yield with 95% ee after only 1 h of irradiation (entry 5). Increasing the amount of MeOH or raising the reaction temperature to 250 °C (entries 6–8) provided no improvement upon that of entry 5. Performing the reaction in the presence of 2 or 1 mol % of the Rh(I)/**1c** catalyst prepared *in situ* from 1 or 0.5 mol %, respectively, of [RhCl(C_2H_4)$_2$]$_2$ resulted in no erosion of the enantioselectivity, but a slight decrease in yield was observed in the latter case (entry 10).

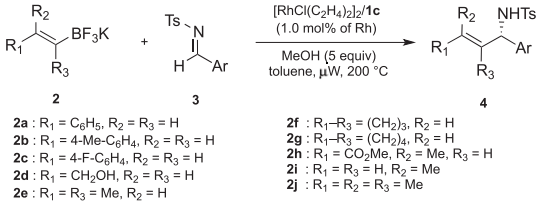
Table 1. Rh(I)-catalyzed asymmetric alkenylation under microwave irradiation



Entry[a]	1 (*x* mol % of Rh)	MeOH (*y* equiv)	Temp (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1[d]	**1a** (3)	5	100	1	70	93
2	**1a** (3)	5	100	3	66	92
3	**1b** (3)	5	100	3	35	94
4	**1c** (3)	5	100	3	72	95
5	**1c** (3)	5	200	1	94	95
6	**1c** (3)	10	200	1	91	93
7	**1c** (3)	20	200	1	94	93
8	**1c** (3)	20	250	0.5	99	92
9	**1c** (2)	5	200	1	94	94
10[e]	**1c** (1)	5	200	1	79	95

[a] Reaction conditions: **2a** (0.250 mmol), **3a** (0.125 mmol), [RhCl(C_2H_4)$_2$]$_2$, (1.87 μmol, 1.5 mol %), ligand **1** (4.50 μmol, 3.6 mol %), MeOH (0.63 mmol), toluene (2.0 mL), reactions were carried out under N_2 in a CEM (Discover and Explorer SP) microwave reactor.
[b] Isolated yield.
[c] Determined by chiral HPLC on an OD-H column.
[d] Preformed [RhCl(**1a**)]$_2$ was used.
[e] The reaction was performed in a 0.25 mmol scale of compound **3a**.

Table 2. Substrate scope of Rh(I)-catalyzed asymmetric alkenylation under microwave irradiation



Entry[a]	2	Ar	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**2a**	C_6H_5 (**3a**)	1	79 [(*S*)-**4aa**]	95
2	**2a**	2-F-C_6H_4 (**3b**)	2	40 [(*S*)-**4ab**]	86
3	**2a**	4-F-C_6H_4 (**3c**)	2	78 [(*S*)-**4ac**]	94
4	**2a**	2-Cl-C_6H_4 (**3d**)	2	55 [(*S*)-**4ad**]	93
5	**2a**	2,4-Cl_2-C_6H_3 (**3e**)	2	67 [(*S*)-**4ae**]	89
6	**2a**	2-Me-C_6H_4 (**3f**)	1	87 [(*S*)-**4af**]	94
7	**2a**	3-Me-C_6H_4 (**3g**)	2	85 [(*S*)-**4ag**]	95
8	**2a**	4-Me-C_6H_4 (**3h**)	1	74 [(*S*)-**4ah**]	93
9	**2a**	4-MeO-C_6H_4 (**3i**)	2	94 [(*S*)-**4ai**]	90
10	**2b**	C_6H_5 (**3a**)	1	92 [(*S*)-**4ba**]	92
11	**2c**	C_6H_5 (**3a**)	1	88 [(*S*)-**4ca**]	94
12	**2d**	C_6H_5 (**3a**)	2	74 [(*S*)-**4da**]	90
13	**2e**	C_6H_5 (**3a**)	1	95 [(*S*)-**4ea**]	93
14	**2e**	2-Me-C_6H_4 (**3f**)	1	95 [(*S*)-**4ef**]	97
15	**2e**	4-Me-C_6H_4 (**3h**)	1	91 [(*S*)-**4eh**]	94
16	**2e**	2-Furyl (**3j**)	1	95 [(*S*)-**4ej**]	95
17	**2e**	2-Thienyl (**3k**)	1	80 [(*S*)-**4ek**]	94
18	**2f**	C_6H_5 (**3a**)	1	96 [(*S*)-**4fa**]	97
19	**2g**	C_6H_5 (**3a**)	1	96 [(*S*)-**4ga**]	95
20	**2g**	2-Me-C_6H_4 (**3f**)	2	90 [(*S*)-**4gf**]	94
21	**2g**	4-Me-C_6H_4 (**3h**)	2	92 [(*S*)-**4gh**]	95
22	**2h**	C_6H_5 (**3a**)	2	89 [(*S*)-**4ha**]	96
23	**2h**	2-Me-C_6H_4 (**3f**)	2	91 [(*S*)-**4hf**]	90
24	**2h**	4-Me-C_6H_4 (**3h**)	2	94 [(*S*)-**4hh**]	96
25	**2i**	C_6H_5 (**3a**)	1	95 [(*S*)-**4ia**]	90
26	**2j**	C_6H_5 (**3a**)	1	95 [(*R*)-**4ja**]	98

[a] General reaction condition: *N*-tosyl aldimines **3** (0.250 mmol), **2** (0.50 mmol), $[RhCl(C_2H_4)_2]_2$ (1.25 μmol, 1 mol% of Rh), ligand **1c** (3.0 μmol, 1.2 mol%), MeOH (1.25 mmol) in toluene (4 mL), reactions were carried out under N_2 in a CEM (Discover and Explorer SP) microwave reactor.
[b] Isolated yield.
[c] Determined by HPLC on a chiral stationary phase.

The scope of the microwave-assisted alkenylation reaction was investigated based on the optimal reaction conditions identified for the asymmetric addition of potassium styryltrifluoroborate (**2a**) to imine (**3a**) established in Table 1 (entry 10). The reactions of trifluoroborate **2a** with aldimines **3b–3e** derived from halogenated aldehydes furnished the addition products **4ab–4ae** in 40–78% yield with 86–94% ee (Table 2, entries 2–5). While the electronic and/or steric effects caused by the presence of *ortho*-chloro or *ortho*-fluoro substituents might have accounted for the observed lower chemical yield and selectivity of entries 2 and 4, the use of *ortho*-tolyl substrate **3f** offered the addition product **4af** in 87% yield with 94% ee (entry 6). Good to high yields and

enantioselectivities were observed for aldimines bearing alkyl and electron-donating substituents (entries 7–9). Enantioselective addition of 1,2-disubstituted alkenyltrifluoroborates with aryl or alkyl substituents (**2b**, R_1 = 4-Me-C_6H_4; **2c**, R_1 = 4-F-C_6H_4; **2d**, R_1 = CH_2OH) to imine **3a** produced the reaction adducts **4ba–4da** in 74–92% yield with 90–94% ee (entries 10–12). Similarly, trisubstituted potassium alkenyltrifluoroborates (**2e**, R_1 = R_3 = Me; **2f**, R_1–R_3 = $(CH_2)_3$; **2g**, R_1–R_3 = $(CH_2)_4$) were good reaction partners, allowing the rapid preparation of enantio-enriched trisubstituted allylic amines **4ea–4gh** with high enantio-enrichment (entries 13–21, 80–96% yield, 93–97% ee), including, notably, (*E*)-chiral allylic amines harboring cyclopentyl (**4fa**) and cyclohexenyl (**4ga**) moieties. The (*E*)-1,3,3-trisubstituted allylic amines **4ha**, **4hf**, and **4hh** (R_1 = CO_2Me, R_2 = Me, R_3 = H) were obtained in 89–94% yield and with 90–96% ee from the asymmetric reaction of alkenyltrifluoroborate **2h**, which bears an ester group at the β-position of the nucleophile (entries 22–24). Crucially, in the thermally heated version of the reaction using the diene ligand **1a**, reaction times of 144–240 h were required for this trifluoroborate, probably due to lower nucleophilicity resulting from the electron-withdrawing carbonyl substituent. By contrast, the microwave-irradiated reaction required only 2 h for a similar conversion. Chiral allylic amine **4ia** harboring (*Z*)-stereochemistry was prepared with 90% ee from the addition of potassium *cis*-propenyltrifluoroborate **2i** in 95% yield, but no cis to trans double-bond isomerization was detected even though the reaction was irradiated at 200 °C (entry 25). Finally, the enantioselective alkenylation of imine **3a** with potassium 3-methyl-2-butenyltrifluoroborate (**2j**) provided the tetra-substituted allylic amine **4ja** in 95% yield and with 98% ee (entry 26) in just 1 h. This is to be compared with the 20 h required when applying the thermal version of the reaction using diene ligand **1a**.

EXPERIMENTAL

To a solution of $[RhCl(C_2H_4)_2]_2$ (1.25 μmol, 1.0 mol% of Rh) and diene ligand **1c** (3.0 μmol, 1.2 mol%) in toluene (4 mL) was added imines **3** (0.25 mmol) and potassium alkenyltrifluoroborates **2** (0.50 mmol). The mixture was stirred for 10 min at room temperature, and then MeOH (50 μL, 1.25 mmol) was added. The reaction mixture was irradiated using a CEM (Discover and Explorer SP) microwave reactor at 200 °C. After thin-layer chromatography (TLC) indicated that consumption of imines **3** was complete, the reaction mixture was cooled to room temperature, diluted with Et_2O (30 mL), and washed with saturated $NaHCO_{3(aq)}$ (10 mL) and then with brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified over silica gel eluting with 8:2 (v/v) hexanes/EtOAc to furnish the alkenylation products **4**.

CONCLUSIONS

The asymmetric 1,2-addition reaction of various potassium alkenyltrifluoroborates with *N*-Ts aldimines under microwave irradiation was realized. The enantioselective transformation proceeded effectively within 1–2 h in the presence of 1 mol % of a Rh(I)-catalyst, generated *in situ* from a Rh(I) dimer precursor and diene ligand **1c**, in a good to highly stereoselective manner to provide a diverse range of optically active di-, tri-, and tetra-substituted chiral allylic amines. By contrast, the previously reported[10] thermal version of the reaction required between 15 and 240 h to reach similar levels of conversion using diene ligand **1a**.

ACKNOWLEDGMENTS

Financial support from Ministry of Science and Technology, Republic of China (102-2113-M-003-006-MY2 and 104-2628-M-003-001-MY3), and National Taiwan Normal University is gratefully acknowledged.

Supporting information

Additional supporting information is available in the online version of this article.

REFERENCES

1. For a review, see: T. C. Nugent Ed., *Chiral Amine Synthesis*, Wiley-VCH, New York, **2008**.
2. For reviews, see: (a) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984; (b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; (c) Johannsen, In *Catalysis in Organic Synthesis*, R. Noyori Ed., Wiley, New York, **1994**; (d) R. B. Cheik, R. Chaabouni, A. Laurent, P. Mison, A. Nafti, *Synthesis* **1983**, *XXX*, 685.
3. For reviews, see: (a) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, *43*, 1461; (b) G. Helmchen, A. Dahnz, P. Dubon, M. Schelwies, R. Weihofen, *Chem. Commun.*

2007, *XXX*, 675; (c) Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258; (d) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164; (e) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; (f) B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327.

4. For reviews, see: (a) H. Nomura, C. J. Richards, *Chem. Asian J.* **2010**, *5*, 1726; (b) M. Calter, T. K. Hollis, L. E. Overman, J. Ziller, G. G. Zipp, *J. Org. Chem.* **1997**, *62*, 1449.
5. (a) E. Skucas, M.-Y. Ngai, V. Komanduri, M. J. Krische, *Acc. Chem. Res.* **2007**, *40*, 1394; (b) S. J. Patel, T. F. Jamison, *Angew. Chem. Int. Ed.* **2004**, *43*, 3941; (c) J.-A. Ma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4290; (d) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991; (e) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539.
6. (a) Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686; (b) S. Lou, S. E. Schaus, *J. Am. Chem. Soc.* **2008**, *130*, 6922; (c) J. A. Bishop, S. Lou, S. E. Schaus, *Angew. Chem. Int. Ed.* **2009**, *48*, 4337; (d) W.-Y. Han, Z.-J. Wu, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2012**, *14*, 976; (e) G. Muncipinto, P. N. Moquist, S. L. Schreiber, S. E. Schaus, *Angew. Chem. Int. Ed.* **2011**, *50*, 8172.
7. (a) K. Brak, J. A. Ellman, *Org. Lett.* **2010**, *12*, 2004; (b) K. Brak, J. A. Ellman, *J. Org. Chem.* **2010**, *75*, 3147; (c) K. Brak, J. A. Ellman, *J. Am. Chem. Soc.* **2009**, *131*, 3850.
8. R. Shintani, M. Takeda, Y.-T. Soh, T. Ito, T. Hayashi, *Org. Lett.* **2011**, *13*, 2977.
9. Y. Luo, A. J. Carnell, H. W. Lam, *Angew. Chem. Int. Ed.* **2012**, *51*, 6762.
10. B. Gopula, C.-W. Chiang, W.-Z. Lee, T.-S. Kuo, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Org. Lett.* **2014**, *16*, 632. Note: the asymmetric alkenylation of *N*-Ns aldimines was subsequently reported by Cui, Z.; Chen, Y.-J.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 1016..
11. (a) N. E. Leadbeater, *Microwave Heating as a Tool for Sustainable Chemistry*, CRC Press, Boca Raton, **2010**; (b) C. O. Kappe, D. Dallinger, S. S. Murphree, *Practical Microwave Synthesis for Organic Chemists*, WILEY-VCH, Weinheim, **2009**; (c) J. Tierney, P. Lidström, *Microwave Assisted Organic Synthesis*, Blackwell Publishing, Oxford, **2007**; (d) E. van der Eycken, C. O. Kappe, *Microwave-Assisted Synthesis of Heterocycles*, Springer, Berlin, **2006**; (e) A. Loupy, *Microwaves in Organic Synthesis*, WILEY-VCH, Weinheim, **2006**; (f) D. Bogdal, *Microwave-assisted Organic Synthesis*, Elsevier, San Diego, **2005**; (g) O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**; (h) P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225; (i) A. de la Hoz, Á. Díaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164; (j) S. Caddick, R. Fitzmaurice, *Tetrahedron* **2009**, *65*, 3325; (k) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279; (l) R. Giguere, L. Bray, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945.
12. (a) T. Ashizawa, S. Tanaka, T. Yamada, *Org. Lett.* **2008**, *10*, 2521; (b) T. Ashizawa, T. Yamada, *Chem. Lett.* **2009**, *XXX*, 246; (c) S. Kikuchi, T. Tsubo, T. Ashizawa, T. Yamada, *Chem. Lett.* **2010**, *XXX*, 574; (d) S. Nushiro, K. Kikuchi, T. Yamada, *Chem. Lett.* **2013**, *XXX*, 165; (e) K. Nushiro, S. Kikuchi, T. Yamada, *Chem. Commun.* **2013**, *49*, 8371.
13. For selected examples of scale-up microwave reactions and its application in pharmaceutical industry, see (a) D. Dallinger, H. Lehmann, J. D. Moseley, A. Stadler, C. O. Kappe, *Org. Process Res. Dev.* **2011**, *15*, 841; (b) H. Lehmann, L. LaVecchia, *Org. Process Res. Dev.* **2010**, *14*, 650; (c) N. E. Leadbeater, V. A. Williams, T. M. Barnard, M. J. Collins, *Org. Process Res. Dev.* **2006**, *10*, 833; (d) F. Bergamelli, M. Iannelli, J. A. Marafie, J. D. Moseley, *Org. Process Res. Dev.* **2010**, *14*, 926; (e) J. R. Schmink, C. A. Kormos, W. G. Devine, N. E. Leadbeater, *Org. Process Res. Dev.* **2010**, *14*, 205; (f) J. D. Moseley, P. Lenden, M. Lockwood, K. Ruda, J.-P. Sherlock, A. D. Thomson, J. P. Gilday, *Org. Process Res. Dev.* **2008**, *12*, 30.
14. J.-F. Syu, Y.-T. Wang, K.-C. Liu, P.-Y. Wu, J. P. Henschke, H.-L. J. Wu, *Org. Chem.* **2016**, *81*, 10832.

