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Kinetic Resolution of Racemic Allylic Alcohols via Catalytic Asymmetric Substitution of the OH Group with Monosubstituted Hydrazines

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Abstract

A new strategy has been established for the kinetic resolution of racemic allylic alcohols through palladium/sulfonyl hydrazide-catalyzed asymmetric substitution of the OH group under mild conditions. In the presence of 1 mol% $[Pd(allyl)Cl]_2$, 4 mol% (*S*)-SegPhos, and 10 mol% 2,5-dichlorobenzenesulfonyl hydrazide, a range of racemic allylic alcohols were smoothly resolved with selectivity factors of up to > 400 via asymmetric allylic alkylation of monosubstituted hydrazines under air at room temperature. Importantly, this kinetic resolution process provided various allylic alcohols and allylic hydrazine derivatives with high enantiopurity.

Main text

Enantioenriched allylic alcohols serve as versatile building blocks in chemical synthesis.[1] Among the great advances to access enantioenriched allylic alcohols, kinetic resolution of racemic ones has emerged as a powerful strategy employed widely in asymmetric synthesis.[2] Technically speaking, the kinetic resolution of racemic allylic alcohols has been accomplished by either epoxidation[3] or electrophilic addition[4] of the C═C bond and by either acylation[5] or oxidation of the OH group (Scheme 1).[6] With regard to racemic terminal allylic alcohols, their kinetic resolution has been developed via iridium-catalyzed asymmetric substitution of the OH group.[7] In addition, racemic allylic alcohols having β-keto,[8] β-ester,[9] or β′-ester groups[10] were reported to be resolved by catalytic processes involving OH elimination or C═C bond hydrogenation. While some of these methods are highly effective in resolving racemic allylic alcohols, it is still highly desirable to develop new methods to expand the scope as well as improve the enantioselectivity. To this end, we have developed a new strategy for efficient kinetic resolution of racemic allylic alcohols through palladium/sulfonyl hydrazide-catalyzed asymmetric substitution of the OH group with monosubstituted hydrazines under air at room temperature (Scheme 1). Decomposition of the sulfonyl hydrazide into a sulfinic acid and a sulfonic acid is essential for the OH group to be substituted smoothly through protonation.

Insert Scheme 1.

Despite the poor leaving ability and compatibility of the OH group, recent years have witnessed a growing interest in the Tsuji-Trost reaction[11] of allylic alcohols.[12] Inspired by previous reports on

the stereospecific intermolecular substitution of enantioenriched allylic alcohols[13] and the kinetic resolution of racemic allylic alcohol derivatives using asymmetric Tsuji-Trost reaction,[14,15] we decided to employ a chiral palladium complex to resolve racemic allylic alcohols despite the great challenge in obviating racemization of π-allylpalladium intermediates as utilized in catalytic asymmetric Tsuji-Trost reaction.[16] We selected carbazates ($ROCONHNH_2$) as nucleophilic components in the Tsuji-Trost reaction of allylic alcohols[17] and the expected kinetic resolution would provide both allylic alcohols and protected allylic hydrazines in enantioenriched form. Notably, very few methods are available to access enantioenriched allylic hydrazine derivatives,[13i,18] which serve as useful building blocks in chemical synthesis.[19] Encouraged by our previous finding that a stoichiometric sulfonyl hydrazide can accelerate the Tsuji-Trost reaction of allylic amines,[20] we decided to survey some sulfonyl hydrazides to identify their abilities to promote the kinetic resolution of racemic allylic alcohols with carbazates.

The model reaction of carbazate **2a** with racemic allylic alcohol ***rac*-1a** proceeded sluggishly in the presence of 1 mol% $[Pd(allyl)Cl]_2$ and 4 mol% (*S*)-SegPhos in dioxane under air at room temperature (Table 1, entry 1). Addition of 50 mol% sulfonyl hydrazide **3a** dramatically accelerated the reaction, and importantly, protected allylic hydrazine **4a** was isolated in 42% yield with 95.1% ee and allylic alcohol **1a** was recovered in 47% yield with 94.8% ee, corresponding to a selectivity factor ($s = k_{fast}/k_{slow}$) of 147 for the kinetic resolution (entry 2).[21] Moreover, the reaction exhibited exclusive α selectivity and complete retention of the *E*-alkene geometry. To our surprise, decreasing the loading of sulfonyl hydrazide **3a** to 10 mol% not only resulted in good conversion but also improved the enantioselectivity with an *s* factor of > 400 (entry 3). The reaction efficiency was affected dramatically by the structure of the sulfonyl hydrazide and the use of a few other sulfonyl hydrazides just led to lower enantioselectivity and/or poor reactivity (entries 4-7). The oxygen in the air proved unnecessary for the reaction to occur but necessary for the high enantioselectivity according to the control experiment performed under nitrogen (entry 8). However, pure oxygen atmosphere also resulted in lower enantioselectivity (entry 9). The use of $Pd(OAc)_2$ as a palladium source decreased the enantioselectivity and even worse, the reaction failed to take place when using $PdCl_2$ and $Pd_2(dba)_3$ (entries 10-12). Replacing (*S*)-SegPhos with axially chiral bisphosphine ligands **L2-5** gave lower enantioselectivity and no desired product was detected in the reaction with chiral monophosphine ligand **L6** or the Trost ligand **L7** (entries 13-18). Finally, we examined a number of common solvents other than dioxane but found lower enantioselectivity and/or poor reactivity (entries 19-22).

Insert Table 1.

In the presence of 1 mol% $[Pd(allyl)Cl]_2$, 4 mol% (*S*)-SegPhos, and 10 mol% sulfonyl hydrazide **3a**, a range of racemic allylic alcohols were resolved through asymmetric allylation of carbazate **2a** under air at room temperature (Table 2, entries 1-22). In general, the reaction with allylic alcohols having α-alkyl groups and γ-aryl (or γ-heteroaryl) groups proceeded with exclusive α selectivity and complete retention of the *E*-alkene geometry and the racemic allylic alcohols were efficiently resolved with *s* factors ranging from 20 to > 400 (entries 1-8 and 10-20). In contrast, lower but still acceptable enantioselectivity was achieved when the α-substituents of allylic alcohols were aryl groups (entries 9 and 22). Unlike the other cases, the allylic moiety of the π-allylpalladium

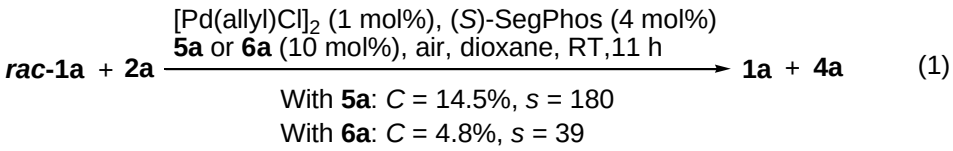
intermediate generated from alcohol ***rac*-1i** is symmetrical, and consequently, the enantiopurity of product **4i** is independent on the enantioselective C─O bond cleavage and determined by the stereoselective attack of the carbazate on the π-allylpalladium. Moreover, the kinetic resolution process was successfully extended to an allylic alcohol having a γ-alkenyl group with excellent enantioselectivity (entry 21). It is noteworthy that the regioselectivity in these cases is determined by the nature of the α- and γ-substituents and the reaction prefers to occur at the allylic position leading to a higher degree of conjugation, which is in accordance with a typical Tsuji-Trost reaction.[11] Nevertheless, the reaction became sluggish with a (*Z*)-allylic alcohol such as (*Z*)-4-phenylbut-3-en-2-ol, with a trisubstituted allylic alcohol such as 4,4-diphenylbut-3-en-2-ol, and a cyclic allylic alcohol such as 2-cyclohexen-1-ol. On the other hand, the reaction proceeded well with a few other carbazates and importantly, excellent enantioselectivity was achieved (entries 23-25). Further investigation revealed that a carbamyl hydrazine, an acyl hydrazide, and a hydrazinylphosphonate were all able to serve as suitable nitrogen nucleophiles in the kinetic resolution reaction of racemic allylic alcohols (entries 26-28). Taken together, this kinetic resolution process permitted the preparation of various allylic alcohols and allylic hydrazine derivatives with high enantiopurity.

Insert Table 2.

To gain insights into the reaction mechanism, we carried out electrospray ionization (ESI) mass spectrometric analysis of the reaction mixture of alcohol ***rac*-1a**, carbazate **2a**, 1 mol% $[Pd(allyl)Cl]_2$, 4 mol% (*S*)-SegPhos, and 10 mol% sulfonyl hydrazide **3a**. According to the high resolution mass data, we tentatively assigned sulfinic acid **5a**, sulfonic acid **6a**, carbazate **7a**, and π-allylpalladiums **8a** and **8b** (Figure 1).[22] We reasoned that π-allylpalladium **8a** was generated by the coordination of (*S*)-SegPhos to $[Pd(allyl)Cl]_2$ and that π-allylpalladium **8b** served as a key intermediate in the Tsuji-Trost reaction (see below). While carbazate **7a** could be generated directly from the reaction of $[Pd(allyl)Cl]_2$ with carbazate **2a**,[23] sulfonyl hydrazide **3a** could accelerate the formation of carbazate **7a** and itself was converted to sulfinic acid **5a**,[20] part of which was subsequently oxidized under air to afford sulfonic acid **6a** (see below).[24]

Insert Figure 1.

Both sulfinic acid **5a** and sulfonic acid **6a** were found to promote the kinetic resolution but with much lower conversion and enantioselectivity relative to the reaction with sulfonyl hydrazide **3a** [Eq. (1)]. These results are in line with the lower enantioselectivity we observed when using a higher loading of sulfonyl hydrazide **3a** or performing the reaction under oxygen (Table 1, entries 2 and 9) because sulfinic acid **5a** and/or sulfonic acid **6a** were generated in higher concentration. In contrast, as demonstrated by the control experiment performed under nitrogen (Table 1, entry 8), lower concentration of sulfinic acid **5a** and/or sulfonic acid **6a** also led to lower conversion and enantioselectivity. Thus, it is plausible to conclude that the use of sulfonyl hydrazide **3a** under air could provide appropriate concentration of sulfinic acid **5a** and/or sulfonic acid **6a** to guarantee good conversion and excellent enantioselectivity.



(1)

Based on the above experimental results and previous relevant studies, we propose the reaction pathways as depicted in Scheme 2. The reaction is initiated by the decomposition of $[Pd(allyl)Cl]_2$ with a monosubstituted hydrazine,[23] which provides Pd(0) and acids needed in the following Tsuji-Trost reaction. Nucleophilic attack of hydrazine derivative **2** (or **3**) on the allylic carbon in $[Pd(allyl)Cl]_2$ affords Pd(0), HCl, and hydrazine derivative **7** (or **9**). Sulfonyl hydrazide **9** is subjected to palladium-catalyzed aerobic oxidation to give sulfonyl diazene **10**, a highly reactive electrophile that undergoes the Tsuji-Trost reaction with monosubstituted hydrazine **2** to give hydrazine derivative **7** and sulfinic acid **5**.[20b] Further oxidation of sulfinic acid **5** gives sulfonic acid **6**.[24] The OH group of racemic allylic alcohol ***rac*-1** is activated by HCl, sulfinic acid **5**, and/or sulfonic acid **6**, and consequently, the allylic C─O bond is cleaved stereoselectively by chiral palladium(0) complex PdL with inversion of configuration to give π-allylpalladium **8**.[13g] Of course, the remaining alcohol **1** is enantioenriched due to the faster consumption of its enantiomer. Nucleophilic attack of monosubstituted hydrazine **2** on the allylic carbon of π-allylpalladium **8** proceeds with inversion of configuration to give allylic hydrazine derivative **4** and regenerate PdL along with the corresponding acid to continue the catalytic cycle. Similar reaction of sulfonyl hydrazide **3** with π-allylpalladium **8** gives sulfonyl hydrazide **11**, aerobic oxidation of which followed by oxidative addition with PdL regenerates π-allylpalladium **8** having a sulfinate anion as a counteranion.

Insert Scheme 2.

In summary, we have developed a new strategy for the kinetic resolution of racemic allylic alcohols through palladium/sulfonyl hydrazide-catalyzed enantioselective C─O bond cleavage under mild conditions. In the presence of 1 mol% $[Pd(allyl)Cl]_2$, 4 mol% (*S*)-SegPhos, and 10 mol% 2,5-dichlorobenzenesulfonyl hydrazide, a range of racemic allylic alcohols were smoothly resolved with selectivity factors of up to > 400 via asymmetric allylic alkylation of monosubstituted hydrazines under air at room temperature. Importantly, this kinetic resolution process proved useful for the preparation of various allylic alcohols and allylic hydrazine derivatives with high enantiopurity.

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References

[1] For reviews, see: a) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry Part B: Reactions and Synthesis, 5th ed.*, Springer, New York, **2007**; b) A. Lumbroso, M. L. Cooke, B. Breit, *Angew. Chem*. **2013**, *125*, 1942-1986; *Angew. Chem. Int. Ed.* **2013**, *52*, 1890-1932.

[2] For reviews, see: a) E. Vedejs, M. Jure, *Angew. Chem*. **2005**, *117*, 4040-4069; *Angew. Chem. Int.*

Ed. **2005**, *44*, 3974-4001; b) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 1613-1666.

[3] a) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240; b) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780; c) P. R. Carlier, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 2978-2979; d) W. Zhang, A. Basak, Y. Kosugi, Y. Hoshino, H. Yamamoto, *Angew. Chem.* **2005**, *117*, 4463-4465; *Angew. Chem. Int. Ed.* **2005**, *44*, 4389-4391; e) J. L. Olivares-Romero, Z. Li, H. Yamamoto, *J. Am. Chem. Soc*. **2013**, *135*, 3411-3413.

[4] M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, R. Bonini, F. Marini, L. Bagnoli, A. Temperini, *Org. Lett.* **2004**, *6*, 4751-4753.

[5] a) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809-1810; b) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493; c) S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun*. **2000**, 1009-1010; d) E. Vedejs, J. A. MacKay, *Org. Lett.* **2001**, *3*, 535-536; e) S. Yamada, T. Misono, Y. Iwai, *Tetrahedron Lett.* **2005**, *46*, 2239-2242; f) T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* **2005**, *7*, 1347-1349; g) V. B. Birman, H. Jiang, *Org. Lett.* **2005**, *7*, 3445-3447; h) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351-1354; i) C. Ó. Dálaigh, S. J. Connon, *J. Org. Chem*. **2007**, *72*, 7066-7069; j) Y. Zhang, V. B. Birman, *Adv. Synth. Catal.* **2009**, *351*, 2525-2529; k) B. Hu, M. Meng, Z. Wang, W. Du, J. S. Fossey, X. Hu, W.-P. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 17041-17044; l) X. Li, H. Jiang, E. W. Uffman, L. Guo, Y. Zhang, X. Yang, V. B. Birman, *J. Org. Chem.* **2012**, *77*, 1722-1737; m) B. Hu, M. Meng, S. Jiang, W. Deng, *Chin. J. Chem.* **2012**, *30*, 1289-1294; n) S. Roy, K.-F. Chen, R. Gurubrahamam, K. Chen, *J. Org. Chem*. **2014**, *79*, 8955-8959; o) S.-S. Jiang, B.-Q. Gu, M.-Y. Zhu, X. Yu, W.-P. Deng, *Tetrahedron* **2015**, *71*, 1187-1191; p) S.-S. Jiang, Q.-C. Xu, M.-Y. Zhu, X. Yu, W.-P. Deng, *J. Org. Chem.* **2015**, *80*, 3159-3169.

[6] a) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, *123*, 7725-7726; b) S. K. Mandal, D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Org. Chem.* **2003**, *68*, 4600-4603; c) J. T. Bagdanoff, B. M. Stoltz, *Angew. Chem.* **2004**, *116*, 357-361; *Angew. Chem. Int. Ed*. **2004**, *43*, 353-357; d) A. T. Radosevich, C. Musich, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 1090-1091; e) V. D. Pawar, S. Bettigeri, S.-S.Weng, J.-Q. Kao, C.-T. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 6308-6309; f) C.-T. Chen, S. Bettigeri, S.-S.Weng, V. D. Pawar, Y.-H. Lin, C.-Y. Liu, W.-Z. Lee, *J. Org. Chem.* **2007**, *72*, 8175-8185; g) D. C. Ebner, R. M. Trend, C. Genet, M. J. McGrath, P. O'Brien, B. M. Stoltz, *Angew. Chem.* **2008**, *120*, 6467-6470; *Angew. Chem. Int. Ed.* **2008**, *47*, 6367-6370; h) R. M. Trend, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 15957-15966; i) D. C. Ebner, J. T. Bagdanoff, E. M. Ferreira, R. M. McFadden, D. D. Caspi, R. M. Trend, B. M. Stoltz, *Chem. Eur. J.* **2009**, *15*, 12978-12992; j) M. A. Fernández-Zúmel, B. Lastra-Barreira, M. Scheele, J. Díez, P. Crochet, J. Gimeno, *Dalton Trans.* **2010**, *39*, 7780-7785; k) T. Kunisu, T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2011**, *133*, 12937-12939; l) K. Ren, L. Zhang, B. Hu, M. Zhao, Y. Tu, X. Xie, T. Y. Zhang, Z. Zhang, *ChemCatChem* **2013**, *5*, 1317-1320; m) H. Mizoguchi, T. Uchida, T. Katsuki, *Angew. Chem.* **2014**, *126*, 3242-3246; *Angew. Chem. Int. Ed.* **2014**, *53*, 3178-3182.

[7] a) M. Roggen, E. M. Carreira, *Angew. Chem*. **2011**, *123*, 5683-5686; *Angew. Chem. Int. Ed*. **2011**, *50*, 5568-5571; b) M. Roggen, E. M. Carreira, *Angew. Chem*. **2012**, *124*, 8780-8783; *Angew. Chem. Int. Ed*. **2012**, *51*, 8652-8655.

[8] a) Y. Wang, X. Feng, H. Du, *Org. Lett.* **2011**, *13*, 4954-4957; b) F. Wang, S. Li, M. Qu, M.-X. Zhao, L.-J. Liu, M. Shi, *Chem. Commun.* **2011**, *47*, 12813-12815.

[9] J. Holz, B. Schäffner, O. Zayas, A. Spannenberg, A. Börner, *Adv. Synth. Catal*. **2008**, *350*, 2533-2543**.**

[10] a) Y. Kim, E. T. Choi, M. H. Lee, Y. S. Park, *Tetrahedron Lett*. **2007**, *48*, 2833-2835; b) M. H. Lee, E. T. Choi, D. Kim, Y. M. Lee, Y. S. Park, *Eur. J. Org. Chem.* **2008**, 5630-5637; c) E. T. Choi, M. H. Lee, Y. Kim, Y. S. Park, *Tetrahedron* **2008**, *64*, 1515-1522; d) E. T. Choi, K. H. Kang, M. H. Lee, Y. S. Park, *Bull. Korean Chem. Soc.* **2008**, *29*, 859-862; e) D. Kim, Y. M. Lee, E. T. Choi, M. H. Lee, Y. S. Park, *Bull. Korean Chem. Soc*. **2009**, *30*, 1211- 1214.

[11] For reviews, see: a) J. Tsuji, *Acc. Chem. Res.* **1969**, *2*, 144-152; b) B. M. Trost, *Tetrahedron* **1977**, *33*, 2615-2649; c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395-422; d) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921-2943; e) U. Kazmaier, M. Pohlman in *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.* (Eds: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 531-583.

[12] For reviews, see: a) Y. Tamaru, *Eur. J. Org. Chem*. **2005**, 2647-2656; b) J. Muzart, *Tetrahedron* **2005**, *61*, 4179-4212; c) J. Muzart, *Eur. J. Org. Chem*. **2007**, 3077-3089; d) M. Bandini, *Angew. Chem.* **2011**, *123*, 1026-1027; *Angew. Chem. Int. Ed.* **2011**, *50*, 994-995; e) B. Sundararaju, M. Achard, C. Bruneau, *Chem. Soc. Rev.* **2012**, *41*, 4467-4483; f) M. Bandini, G. Cera, M. Chiarucci, *Synthesis* **2012**, *44*, 504-512; g) N. A. Butt, W. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 7929-7967.

[13] a) F. Ozawa, H. Okamoto, S. kawagishi, S. Yamamoto, T. Minami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 10968-10969; b) Y. S. Vikhe, S. M. Hande, N. Kawai, J. Uenishi, *J. Org. Chem.* **2009**, *74*, 5174-5180; c) M. Roggen, E. M. Carreira, *J. Am. Chem. Soc*. **2010**, *132*, 11917-11919; d) P. Mukherjee, R. A. Widenhoefer, *Org. Lett*. **2010**, *12*, 1184-1187; e) P. Mukherjee, R. A. Widenhoefer, *Chem. Eur. J*. **2013**, *19*, 3437-3444; f) J. Ye, J. Zhao, J. Xu, Y. Mao, Y. J. Zhang, *Chem. Commun.* **2013**, *49*, 9761-9763; g) H.-B. Wu, X.-T. Ma, S.-K. Tian, *Chem. Commun*. **2014**, *50*, 219-221; h) X.-T. Ma, R.-H. Dai, J. Zhang, Y. Gu, S.-K. Tian, *Adv. Synth. Catal.* **2014**, *356*, 2984-2988; i) J.-K. Xu, Y. Gu, S.-K. Tian, *Chin. J. Org. Chem.* **2015**, 35, 618-624.

[14] a) T. Hayashi, A. Yamamoto, Y. Ito, *J. Chem. Soc., Chem. Commun.* **1986**, 1090-1092; b) S. Ramdeehul, P. Dierkes, R. Aguado, P. C. J. Kamer, P.W. N. M. van Leeuwen, J. A. Osborn, *Angew. Chem.* **1998**, *110*, 3302-3304; *Angew. Chem. Int. Ed.* **1998**, *37*, 3118-3121; c) Y. K. Choi, J. H. Suh, D. Lee, I. T. Lim, J. Y. Jung, M.-J. Kim, *J. Org. Chem.* **1999**, *64*, 8423-8424; d) H.-J. Gais, N. Spalthoff, T. Jagusch, M. Frank, G. Raabe, *Tetrahedron Lett.* **2000**, *41*, 3809-3812; e) J. M. Longmire, B. Wang, X. Zhang, *Tetrahedron Lett*. **2000**, *41*, 5435-5439; f) H.-J. Gais, T. Jagusch, N. Spalthoff, F. Gerhards, M. Frank, G. Raabe, *Chem. Eur. J.* **2003**, *9*, 4202-4221; g) B. J. Lüssem, H.-J. Gais, *J. Am. Chem. Soc*. **2003**, *125*, 6066-6067; h) J. W. Faller, J. C. Wilt, J. Parr, *Org. Lett.* **2004**, *6*, 1301-1304; i) S. Jansat, M. Gómez, K. Philippot, G. Muller, E. Guiu, C. Claver, S. Castillón, B. Chaudret, *J. Am. Chem. Soc.* **2004**, *126*, 1592-1593; j) H.-J. Gais, O. Bondarev, R. Hetzer, *Tetrahedron Lett.* **2005**, *46*, 6279-6283; k) P. Gonzalez-Bulnes, J. Casas, A. Delgado, A. Llebaria, *Carbohydr. Res.* **2007**, *342*, 1947-1952; l) T. Mino, K. Wakui, S. Oishi, Y. Hattori, M. Sakamoto, T. Fujita, *Tetrahedron: Asymmetry* **2008**, *19*, 2711-2716; m) A. Rosas-Hernández, E. Vargas-Malvaez, E. Martin, L. Crespi, J. C. Bayón, *J. Mol. Catal. A: Chem.* **2010**, *328*, 68-75; n) B. Mao, Y. Ji, M. Fañanás-Mastral, G. Caroli, A. Meetsma, B. L. Feringa, *Angew. Chem*. **2012**, *124*, 3222-3227; *Angew. Chem. Int. Ed.* **2012**, *51*, 3168-3173; o) K. Ulbrich, P. Kreitmeier, T. Vilaivan, O. Reiser, *J. Org. Chem*. **2013**, *78*, 4202-4206; p) D.-C. Bai, W.-Y. Wang, C.-H. Ding, X.-L. Hou, *Synlett* **2015**, *26*, 1510-1514.

[15] For similar transition metal-catalyzed kinetic resolution of racemic allylic alcohol derivatives, see: a) D. L. Hughes, M. Palucki, N. Yasuda, R. A. Reamer, P. J. Reider, *J. Org. Chem.* **2002,** *67*, 2762-2768; b) C. Fischer, C. Defieber, T. Suzuki, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629; c) K. Onitsuka, Y. Matsushima, S. Takahashi, *Organometallics* **2005**, *24*, 6472-6474; d) X.-B. Jiang, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2007**, 2287-2289; e) D. C. Vrieze, G. S. Hoge, P. Z. Hoerter, J. T. Van Haitsma, B. M. Samas, *Org. Lett.* **2009**, *11*, 3140-3142.

[16] a) D. Banerjee, K. Junge, M. Beller, *Angew. Chem*. **2014**, *126*, 13265-13269; *Angew. Chem. Int. Ed*. **2014**, *53*, 13049-13053; b) X. Huo, G. Yang, D. Liu, Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem*. **2014**, *126*, 6894-6898; *Angew. Chem. Int. Ed*. **2014**, *53*, 6776-6780**.**

[17] S. Tšupova, U. Mäeorg, *Org. Lett.* **2013**, *15*, 3381-3383.

[18] a) T. Yamagishi, M. Ohnuki, T. Kiyooka, D. Masui, K. Sato, M. Yamaguchi, *Tetrahedron: Asymmetry* **2003**, *14*, 3275-3279; b) R. J. Kloetzing, P. Knochel, *Tetrahedron: Asymmetry* **2006**, *17*, 116-123; c) D. Popa, R. Marcos, S. Sayalero, A. Vidal-Ferran, M. A. Pericàs, *Adv. Synth. Catal*. **2009**, *351*, 1539-1556; d) H. Yuan, Z. Zhou, J. Xiao, L. Liang, L. Dai, *Tetrahedron: Asymmetry* **2010**, *21*, 1874-1884; e) K. E. Lutz, R. J. Thomson, *Angew. Chem.* **2011**,*123*, 4529-4532; *Angew. Chem. Int. Ed*. **2011**, *50*, 4437-4440; f) Y. Wang, J.-K. Xu, Y. Gu, S.-K. Tian, *Org. Chem. Front.* **2014**, *1*, 812-816.

[19] a) B. F. Strick, D. A. Mundal, R. J. Thomson, *J. Am. Chem. Soc*. **2011**, *133*, 14252-14255; b) O. Gutierrez, B. F. Strick, R. J. Thomson, D. J. Tantillo, *Chem. Sci*. **2013**, *4*, 3997-4003; c) J. C. T. Reddel, K. E. Lutz, A. B. Diagne, R. J. Thomson, *Angew. Chem.* **2014**, *126*, 1419-1422; *Angew. Chem. Int. Ed*. **2014**, *53*, 1395-1398.

[20] a) Y. Wang, Y.-N. Xu, G.-S. Fang, H.-J. Kang, Y. Gu, S.-K. Tian, *Org. Biomol. Chem.* **2015**, *13*, 5367-5371; b) T.-T. Wang, F.-X. Wang, F.-L. Yang, S.-K. Tian, *Chem. Commun.* **2014**, *50*, 3802-3805.

[21] For calculation of *s* factors, see: H. B. Kagan, J. C. Fiaud, *Top. Stereochem*. **1988**, *18*, 249-330. As suggested by one reviewer, the exact *s* values were not given when they were > 400 because of big errors.

[22] For details, see the Supporting Information.

[23] Y.-H. Su, Z. Wu, S.-K. Tian, *Chem. Commun*. **2013**, *49*, 6528-6530.

[24] A. Deavin, C. W. Rees, *J. Chem. Soc.* **1961**, 4970-4973.

Scheme legends

Scheme 1. Strategies for the kinetic resolution of racemic allylic alcohols.

Scheme 2. Proposed reaction pathways.

Figure legends

Figure 1. Some intermediates and byproducts.

Tables

Table 1. Optimization of reaction conditions.[a]

Entry	**3**	R	[Pd]	L	Solvent	Yield [%][b]		*ee* [%][c]		*C* [%][d]	*s*[e]
						1a	**4a**	**1a**	**4a**		

1	—	none	$[Pd(allyl)Cl]_2$	**L1**	dioxane	—	trace	—	—	—	—
2[f]	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	47	42	94.8	95.1	49.9	147
3	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	49	44	99.5	98.3	50.3	> 400
4	**3b**	2,4,6-$Me_3C_6H_2$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	47	42	96.0	96.3	49.9	210
5	**3c**	4-$MeOC_6H_4$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	—	trace	—	—	—	—
6	**3d**	4-$O_2NC_6H_4$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	82	5	5.7	98.8	—	—
7	**3e**	$PhCH_2$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	88	2	3.0	98.7	—	—
8[g]	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	52	38	72.0	98.2	42.3	239
9[h]	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	dioxane	46	40	98.7	96.7	50.5	300
10	**3a**	2,5-$Cl_2C_6H_3$	$Pd(OAc)_2$	**L1**	dioxane	46	48	99.4	95.1	51.1	230
11	**3a**	2,5-$Cl_2C_6H_3$	$PdCl_2$	**L1**	dioxane	—	0	—	—	—	—
12	**3a**	2,5-$Cl_2C_6H_3$	$Pd_2(dba)_3$	**L1**	dioxane	—	0	—	—	—	—
13	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L2**	dioxane	45	46	97.1	86.2	53.0	57
14	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L3**	dioxane	46	49	94.6	86.1	52.4	48
15	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L4**	dioxane	45	48	99.6	82.8	54.6	64
16	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L5**	dioxane	49	47	91.7	92.7	49.7	86
17	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L6**	dioxane	—	0	—	—	—	—
18	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L7**	dioxane	—	0	—	—	—	—
19	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	tetrahydrofuran	47	48	97.8	97.2	50.2	319
20	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	toluene	41	52	95.7	84.4	53.1	45
21	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	ethyl acetate	46	48	96.9	95.7	50.3	191
22	**3a**	2,5-$Cl_2C_6H_3$	$[Pd(allyl)Cl]_2$	**L1**	solvent[i]	—	trace	—	—	—	—

[a] Reaction conditions: ***rac*-1a** (0.20 mmol), **2a** (0.16 mmol), **3** (10 mol%), [Pd] (1 mol%), L (4 mol%), solvent (0.50 mL), air (1 atm), RT, 11 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] C (conversion) = $ee_{1a}/(ee_{1a} + ee_{4a})$. [e] $s = \ln[(1 - C)(1 - ee_{1a})]/\ln[(1 - C)(1 + ee_{1a})]$.[21] [f] 50 mol% **3a** was used. [g] The reaction was run under nitrogen. [h] The reaction was run under oxygen. [i] 1,2-Dichloroethane, acetonitrile, *N*,*N*-dimethylformamide, or dimethyl sulfoxide. Ac = acetyl, dba = dibenzylideneacetone.

Table 2. Kinetic resolution of racemic allylic alcohols.[a]

Entry	**1**	R^1	R^2	**2**	R^3	**4**	t [h]	Yield [%][b]		*ee* [%][c]		C [%][d]	s[e]
								1	**4**	**1**	**4**		
1	**1a**	Ph	$CHMe_2$	**2a**	Cbz	**4a**	11	49	44	99.5	98.3	50.3	> 400
2	**1b**	Ph	cyclopentyl	**2a**	Cbz	**4b**	11	42	42	99.7	93.5	51.6	192
3	**1c**	Ph	cyclohexyl	**2a**	Cbz	**4c**	11	49	40	99.7	97.7	50.5	> 400

4	**1d**	Ph	Me	**2a**	Cbz	**4d**	4	43	54	88.7	75.4	54.1	21
5	**1e**	Ph	CH_2CHMe_2	**2a**	Cbz	**4e**	8	46	41	88.1	88.5	49.9	48
6	**1f**	Ph	$(CH_2)_7Me$	**2a**	Cbz	**4f**	6	39	43	97.2	68.6	58.6	22
7	**1g**	Ph	CH_2CH_2Ph	**2a**	Cbz	**4g**	8	44	43	97.0	84.2	53.5	48
8	**1h**	Ph	$CH_2CH=CH_2$	**2a**	Cbz	**4h**	24	43	25	96.3	78.6	55.1	33
9	**1i**	Ph	Ph	**2a**	Cbz	**4i**	10	49	42	94.2	52.7	—	—
10	**1j**	4-FC_6H_4	$CHMe_2$	**2a**	Cbz	**4j**	11	47	42	98.6	97.2	50.4	350
11	**1k**	4-ClC_6H_4	$CHMe_2$	**2a**	Cbz	**4k**	11	48	44	99.9	94.2	51.5	252
12	**1l**	4-BrC_6H_4	$CHMe_2$	**2a**	Cbz	**4l**	11	48	42	97.8	95.6	50.6	201
13	**1m**	4-NCC_6H_4	$CHMe_2$	**2a**	Cbz	**4m**	4	52	40	85.3	95.8	47.1	128
14	**1n**	4-$MeOC_6H_4$	$CHMe_2$	**2a**	Cbz	**4n**	11	54	42	78.1	97.3	44.5	174
15	**1o**	3-MeC_6H_4	$CHMe_2$	**2a**	Cbz	**4o**	11	44	44	99.3	92.0	51.9	134
16	**1p**	2-$MeOC_6H_4$	$CHMe_2$	**2a**	Cbz	**4p**	14	50	37	86.7	97.6	47.0	234
17	**1q**	1-naphthyl	$CHMe_2$	**2a**	Cbz	**4q**	14	47	40	96.2	97.1	49.8	272
18	**1r**	2-naphthyl	$CHMe_2$	**2a**	Cbz	**4r**	16	50	44	91.2	95.4	48.9	136
19	**1s**	2-furyl	$CHMe_2$	**2a**	Cbz	**4s**	24	56	31	67.3	97.8	40.8	182
20	**1t**	3-thienyl	$CHMe_2$	**2a**	Cbz	**4t**	12	50	46	94.9	98.8	49.0	> 400
21	**1u**	(*E*)-PhCH=CH	$CHMe_2$	**2a**	Cbz	**4u**	18	70	21	39.6	96.4	29.1	81
22	**1v**	Me	Ph	**2a**	Cbz	**4b**	11	57	39	43.1	60.3	41.7	6
23	**1a**	Ph	$CHMe_2$	**2b**	Boc	**4ab**	9	46	47	98.6	97.5	50.3	393
24	**1a**	Ph	$CHMe_2$	**2c**	Fmoc	**4ac**	13	46	44	97.7	98.8	49.7	> 400
25	**1a**	Ph	$CHMe_2$	**2d**	CO_2Et	**4ad**	8	48	48	97.4	98.6	49.7	> 400
26	**1a**	Ph	$CHMe_2$	**2e**	CONHPh	**4ae**	13	48	46	97.5	94.6	50.8	158
27	**1a**	Ph	$CHMe_2$	**2f**	COPh	**4af**	21	61	34	46.5	78.6	37.2	13
28	**1a**	Ph	$CHMe_2$	**2g**	$PO(OEt)_2$	**4ag**	11	67	27	45.1	95.3	32.1	65

[a] Reaction conditions: ***rac*-1** (0.20 mmol), **2** (0.16 mmol), **3a** (10 mol%), $[Pd(allyl)Cl]_2$ (1 mol%), (*S*)-SegPhos (4 mol%), dioxane (0.50 mL), air (1 atm), RT, 4-24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $C = ee_1/(ee_1 + ee_4)$. [e] $s = \ln[(1 - C)(1 - ee_1)]/\ln[(1 - C)(1 + ee_1)]$. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl.

Text for the Table of Contents

Eye-catching headline: Kinetic Resolution

Liang Yan, Jing-Kun Xu, Chao-Fan Huang, Zeng-Yang He, Ya-Nan Xu, and Shi-Kai Tian*

Kinetic Resolution of Racemic Allylic Alcohols via Catalytic Asymmetric Substitution of the OH Group with Monosubstituted Hydrazines

Insert TOC

A range of racemic allylic alcohols were resolved with selectivity factors of up to > 400 via palladium/sulfonyl hydrazide-catalyzed asymmetric allylation of monosubstituted hydrazines under air at room temperature (see scheme). The reaction provided various allylic alcohols and allylic hydrazine derivatives with high enantiopurity.

Keywords: allylic alcohols • allylic hydrazines • kinetic resolution • palladium • sulfonyl hydrazides