Cycloaddition

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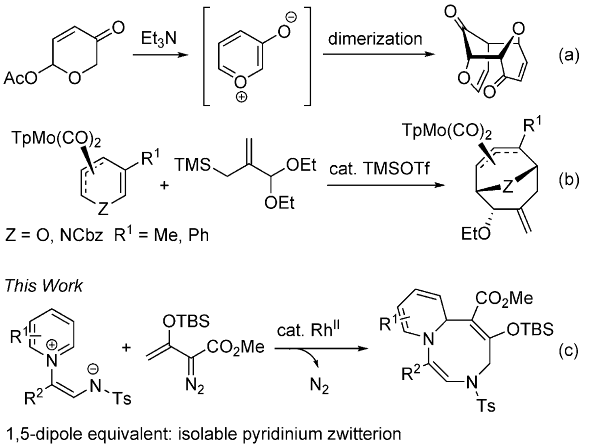
Rhodium(II)-Catalyzed Cycloaddition Reactions of Non-classical 1,5-Dipoles for the Formation of Eight-Membered Heterocycles

*Dong Jin Lee, Donguk Ko, and Eun Jeong Yoo**

Abstract: *A new type of intermolecular rhodium(II)-catalyzed [5+3] cycloaddition has been developed. This higher-order cycloaddition between pyridinium zwitterion 1,5-dipole equivalents and enol diazoacetates enables the formation of eight-membered heterocyclic skeletons, which are otherwise difficult to construct. The optimized cycloaddition occurs efficiently under mild conditions with a wide range of pyridinium zwitterions and with high functional-group tolerance.*

Dipolar cycloaddition has become a powerful strategy for synthesizing heterocyclic compounds in a single operation without giving rise to byproducts.[1] While most previous studies have mainly focused on [3+2] cycloaddition by using the well-established 1,3-dipoles to react with 2π-dipolarophiles, studies to employ additional variants such as 1,2-, 1,4-, or 1,5-dipoles for forming heterocyclic compounds with ring sizes other than five are limited.[2] For instance, 2-alkyl-2,3-butadienoate, a 1,4-dipole synthon, was employed for [4+2] cycloaddition, thereby resulting in the construction of six-membered heterocycles,[3a] and 2-arylcyclopropane-1,1-dicarboxylate, an atypical 1,2-dipole source, was found to dimerize to afford tetralin through a similar cycloaddition.[3b] These examples clearly demonstrate that with a compatible match between the dipole and dipolarophile counterparts, not only the cyclic scaffold but also the complexity of products can be controlled; hence, the development of novel 1,*n*-dipoles is in high demand.

Eight-membered heterocycles are one of the most prominent classes of compounds and make up the structural core in a large number of biologically important natural products and pharmaceuticals.[4] Although higher-order cycloaddition is an extraordinary tool for the formation of medium-sized heterocycles in a single operation,[5] eight-membered cyclic compounds are generally synthesized by cross-coupling reactions, the Heck reaction, or ring-closing metathesis owing to hindered enthalpic and entropic factors associated with higher-order cycloaddition. Only a few pioneering studies of [5+3] cycloaddition for affording eight-membered heterocycles have been reported. In 1980, Hendrickson et al. reported that a 3-oxidopyrylium zwitterionic intermediate, generated in situ from acetoxypyranone, readily undergoes dimerization to afford a doubly bridged eight-membered heterocyclic compound (Scheme 1 a).[6a] Liebeskind et al. have developed a Lewis acid catalyzed [5+3] cycloaddition between molybdenum π complexes and allylic acetals, resulting in oxa- and aza-[3.3.1]bicyclic complexes (Scheme 1 b).[6b] Although other methods have been reported for the formation of in situ generated 1,5-zwitterionic intermediates,[7] studies of intermolecular cycloaddition for synthesizing eight-membered-ring compounds are rather limited. Herein, we report a new type of [5+3] cycloaddition of an isolable pyridinium zwitterion with enol diazoacetate to afford diazocine derivatives, which are valuable eight-membered N-heterocyclic compounds. (Scheme 1 c).



Scheme 1. [5+3] Cycloaddition reactions.

The Doyle group has extensively investigated Rh^{II}-catalyzed $[3+n]$ cycloaddition between enol diazoacetates, which are precursors of rhodium(II) enolcarbene,[8] and 1,3-dipoles, such as nitrone,[9a] *N*-iminopyrinium ylide,[9b] and isoquinolinium ylide,[9c] for the preparation of five- and six-membered-ring compounds. Recently, our group revealed an unprecedented pyridinium zwitterion that can be isolated and exhibits patterns of charge distribution different from those exhibited by typical pyridinium ylides.[10] Intrigued by the high reactivity of rhodium(II) enolcarbene, we envisioned that the stable zwitterion would undergo annulation with rhodium(II) enolcarbene via [5+3] cycloaddition to afford an eight-membered heterocyclic compound.

With these considerations in mind, we initiated our investigation of Rh^{II}-catalyzed cycloaddition with enol diazoacetate (**2**) by evaluating the efficiency of stable pyridinium zwitterions for cycloaddition (Table 1). First, the reaction was conducted with pyridinium zwitterion **1a** and various enol diazoacetates (**2**) using 2.0 mol % of the Rh^{II} catalyst at room temperature. Triisopropylsilyl (TIPS)- and tert-butyldime-

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[*] D. J. Lee, D. Ko, Prof. E. J. Yoo
Department of Chemistry, Kangwon National University
1 Kangwondaehak-gil, Chuncheon, 200-701 (Republic of Korea)
E-mail: ejyoo@kangwon.ac.kr

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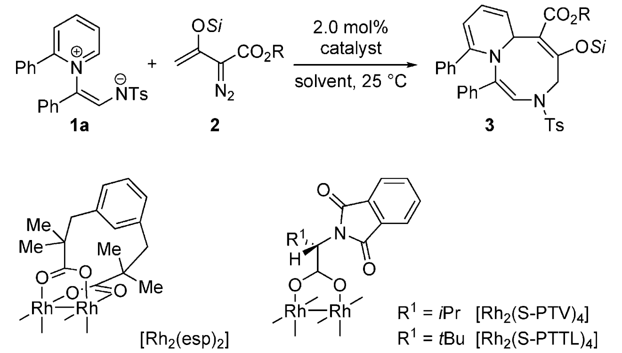
Table 1: Optimization of Reaction Conditions.[a]



Entry	Catalyst	R/*Si* (**2**)	Solvent	Yield [%][b]
1	[$Rh_2(esp)_2$]	*t*Bu/TIPS	1,2-DCE	5
2	[$Rh_2(esp)_2$]	Me/TIPS	1,2-DCE	10
3	[$Rh_2(esp)_2$]	*t*Bu/TBS	1,2-DCE	40
4	[$Rh_2(esp)_2$]	Me/TBS	1,2-DCE	39 (**3a**)
5	[Rh_2(S-PTTL)$_4$]	Me/TBS	1,2-DCE	22
6	[Rh_2(S-PTV)$_4$]	Me/TBS	1,2-DCE	30
7	[$Rh_2(OPiv)_4$]	Me/TBS	1,2-DCE	40
8	[$Rh_2(OPiv)_4$]	Me/TBS	CH_2Cl_2	43
9	[$Rh_2(OPiv)_4$]	Me/TBS	CH_2Cl_2	64[c]
10	[$Rh_2(OPiv)_4$]	Me/TBS	CH_2Cl_2	6[d]
11	[$Rh_2(OPiv)_4$]	Me/TBS	CH_2Cl_2	27[e]

[a] Reaction conditions: **1a** (0.2 mmol), enol diazoacetate (**2**, 3.0 equiv), catalyst (2.0 mol%), and solvent (1.0 mL) at 25 °C. [b] ^{1}H NMR yields of **3** using CH_2Br_2 as the internal standard. [c] 4 Å M.S. (40 mg) was added. [d] Reaction was conducted at 0 °C. [e] Reaction was conducted at 60 °C.

thylsilyl (TBS)-protected enol diazoacetates afforded full conversion, albeit with comparatively varied yields of the corresponding cyclic products (**3**). From the NMR data and single-crystal X-ray analysis, the obtained cyclic compound was clearly confirmed to be an eight-membered heterocyclic compound (Figure 1).[11]

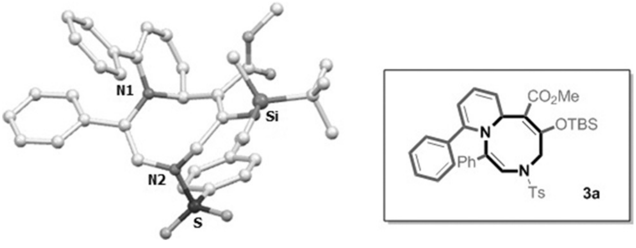
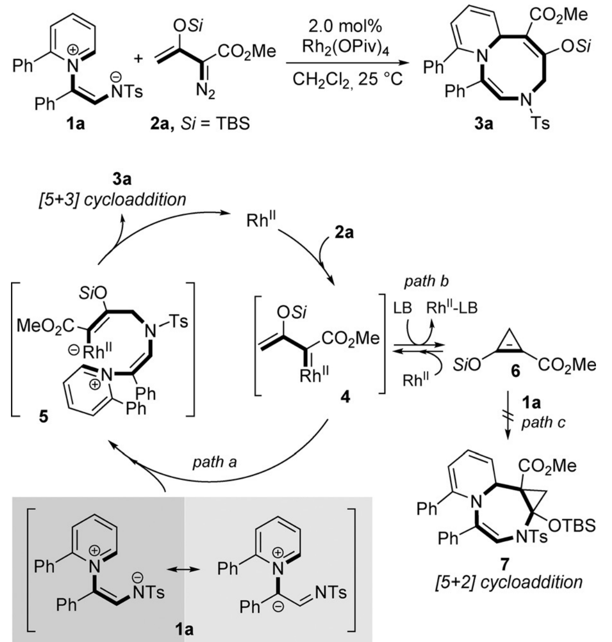


Figure 1. X-ray structure of [5+3]-cyclized product **3a**.

As shown in Table 1, on changing the protecting group of **2** from TIPS to TBS, the yield of [5+3]-cyclized product **3** typically increased (entries 1–4). Among the examined rhodium catalysts,[12] the reaction with [$Rh_2(OPiv)_4$] catalyst in a chlorinated solvent generated the desired product **3a** in at least 40% yield (entries 7 and 8). The addition of 4 Å M.S. to the reaction mixture increased the yield of **3a** up to 64% (entry 9).[13] Temperature was also found to affect the reactivity of the cycloaddition of the pyridinium zwitterion; the product yield dramatically decreased when the reaction was conducted at 0 °C (entry 10). High temperature also led to poor yield (entry 11).

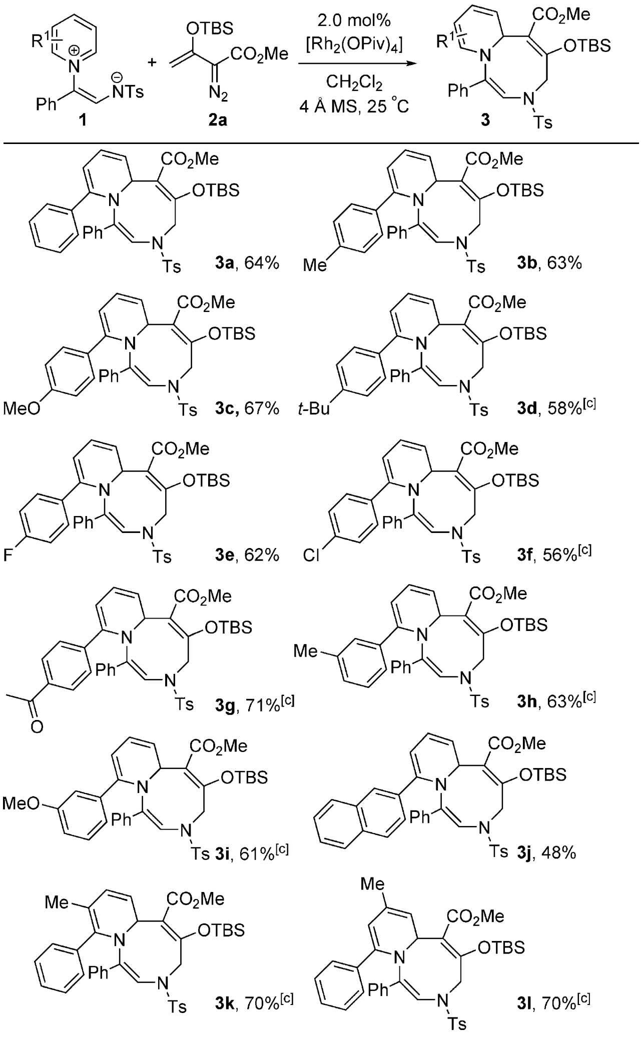
While further investigation of this zwitterion in the role of a 1,5-dipole remains, the possible reaction pathway can be postulated as shown in Scheme 2. The first step involves the loss of nitrogen gas from enol diazoacetate **2a** to generate rhodium(II) enolcarbene **4**, which has electrophilic reaction sites at both the metal–carbene and vinylogous positions.[9c] Then, nucleophilic attack of pyridinium zwitterion **1a** on the vinylogous position of rhodium(II) enolcarbene **4** occurs (*path a*), followed by intramolecular cyclization to give the eight-membered-ring product **3a**. Because the nitrogen atom of the participating zwitterion **1a** exhibits nucleophilicity greater than that of the carbon atom in the related pyridinium ylide,[9c,14] zwitterion **1a** possibly participates in cycloaddition as an unprecedented 1,5-dipole equivalent (*path a*). On the other hand, rhodium(II) compounds are mild Lewis acids that coordinate with Lewis bases, thereby causing the rearrangement of **4** to generate cyclopropene **6** (*path b*).[9c] Interestingly, although the addition of a Lewis base such as CH_3CN promoted the production of **6** and decreased the yield of the product, [5+2] cycloaddition between pyridinium zwitterion **1a** and cyclopropene **6** (*path c*) was not observed, presumably because of the the distinct nature of the pyridinium zwitterion as a dipole compared with that of 1,3-dipoles.



Scheme 2. Mechanistic pathway for the Rh^{II}-catalyzed cycloaddition of pyridinium zwitterion.

With the above mechanistic insights, reactions of various pyridinium zwitterion derivatives (**1**) with TBS-protected enol diazoacetate (**2a**) were conducted under the optimized reaction conditions to examine the scope of the [5+3] cycloaddition. As shown in Table 2, variation of the pyridinium backbone of the zwitterion did not significantly affect the efficiency of the cycloaddition. Substrates with *para*- or *meta*-substituted aryl groups at the C position of the pyridinium

Table 2: Rh^{II}-catalyzed [5+3]-cycloaddition of pyridinium zwitterions.[a,b]



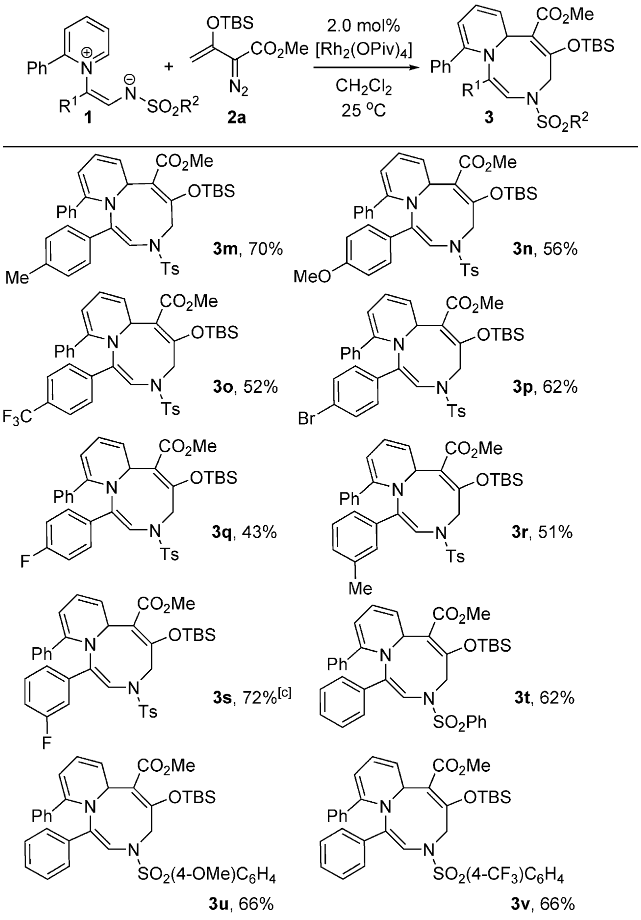
[a] Reaction conditions: **1** (0.1 mmol), enol diazoacetate **2a** (3.0 equiv), [Rh$_2$(OPiv)$_4$] (2.0 mol%), 4 Å M.S. (40 mg), and CH$_2$Cl$_2$ (1.0 mL) at 25 °C. [b] Yield of isolated product. [c] Without 4 Å M.S..

moiety readily reacted, affording the desired products in good yields.

Both halide and ketone functional groups were tolerated under the reaction conditions to afford the corresponding products **3e**–**3g**. The reaction with a naphthyl-containing zwitterion furnished the cyclic product **3j** under the optimized conditions, albeit in somewhat low yield (48%). Moreover, zwitterions possessing difunctionalized pyridinium backbones smoothly underwent [5+3] cycloaddition in a facile manner, affording **3k** and **3l** in 70% yields.

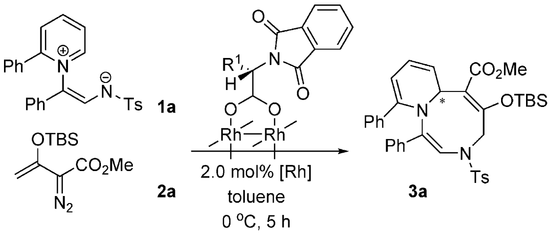
[5+3] Cycloaddition was subsequently applied to a range of 1,5-dipole equivalents with modification of the N-sulfonyl enamide moieties of the pyridinium zwitterions (Table 3). Pleasingly, most of the zwitterions with *para* substituents, including alkyl, alkoxy, and halide substituents, were found to be compatible with enol diazoacetate **2a** and furnished the desired products **3m**–**3q** in moderate yields (43–70%). This cyclization efficiency was not significantly affected by the steric hindrance of the substrates (**3r** and **3s**). In addition, the electronic variation of the N-sulfonyl group also did not affect cycloaddition and furnished the corresponding products **3t**–**3v**.

Table 3: Rh^{II}-catalyzed [5+3]-cycloaddition of pyridinium zwitterions.[a,b]



[a] Reaction conditions: **1** (0.1 mmol), enol diazoacetate **2a** (3.0 equiv), [Rh$_2$(OPiv)$_4$] (2.0 mol%), and CH$_2$Cl$_2$ (1.0 mL) at 25 °C. [b] Yield of isolated product. [c] 4 Å M.S. (40 mg) added.

To demonstrate synthetic utility, the stereoselective [5+3] cycloaddition of **1a** with TBS-protected enol diazoacetate **2a** was attempted. It was envisioned that asymmetric induction would be enhanced by tuning the steric environment of the chiral ligands of the rhodium(II) catalyst. We were pleased to observe that high enantiometric excess (90%) was achieved when the cycloaddition was catalyzed by [Rh$_2$(S-PTAD)$_4$] in toluene at 0 °C [(Eq. (1)].



(1)

R^1 = *i*Pr; [Rh$_2$(S-PTV)$_4$] 47%, 62% ee
R^1 = *t*Bu; [Rh$_2$(S-PTTL)$_4$] 23%, 67% ee
R^1 = 1-adamantyl; [Rh$_2$(S-PTAD)$_4$] 63%, 90% ee

In summary, we have developed a new catalytic [5+3] cycloaddition between isolable pyridinium zwitterions and enol diazoacetates. This cycloaddition enables the facile construction of eight-membered heterocyclic compounds that are otherwise difficult to access. Studies to apply pyridinium zwitterions to additional synthetic approaches are currently underway.

Experimental Section

To a test tube with a triangular stir bar were added pyridinium zwitterion (**1**, 0.1 mmol), [$Rh_2(OPiv)_4$] (2.0 mol %), and CH_2Cl_2 (1.0 mL) under N_2 atmosphere. A solution of TBS-protected enol diazoacetate (**2a**, 3.0 equiv) in CH_2Cl_2 (0.5 mL) was added to the reaction mixture through a syringe pump. The reaction mixture was stirred at room temperature, filtered through a pad of celite and then washed with CH_2Cl_2 (10 mL × 3). Organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel to give the desired product **3**.

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[1] a) X. Xu, M. P. Doyle, *Acc. Chem. Res.* **2014**, *47*, 1396; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863; c) *1,3-Dipolar Cycloaddition Chemistry*, *Vol. 1 & 2* (Ed.: A. Padwa), Wiley, New York, **1984**, p. 1521.

[2] Selected references for 1,2- and 1,4-dipole precursors: a) R. Huisgen in *Topics in Heterocyclic Chemistry* (Ed.: R. Castle), Wiley, New York, **1969**, chap. 8; b) A. Padwa, S. R. Harring, M. A. Semones, *J. Org. Chem.* **1998**, *63*, 44; c) I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Chem. Commun.* **2001**, 958; d) V. Nair, A. R. Sreekanth, N. Abhilash, M. M. Bhadbhade, R. C. Gonnade, *Org. Lett.* **2002**, *4*, 3575; e) B. Alcaide, P. Almendros, I. Fernández, C. Lázaro-Milla, *Chem. Commun.* **2015**, *51*, 3395; f) Y. Li, X. Su, W. Zhou, W. Li, J. Zhang, *Chem. Eur. J.* **2015**, *21*, 4224.

[3] a) X.-F. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716; b) R. A. Novikov, A. V. Tarasova, V. A. Korolev, V. P. Timofeev, Y. V. Tomilov, *Angew. Chem. Int. Ed.* **2014**, *53*, 3187; *Angew. Chem.* **2014**, *126*, 3251.

[4] Recent review: K. C. Majumdar, *RSC Adv.* **2011**, *1*, 1152.

[5] Selected references: a) P. A. Wender, A. G. Correa, Y. Sato, R. Sun, *J. Am. Chem. Soc.* **2000**, *122*, 7815; b) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 9512; *Angew. Chem.* **2012**, *124*, 9650; c) Z.-L. He, H.-L. Teng, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2934; *Angew. Chem.* **2013**, *125*, 3006; d) Z.-L. He, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 534.

[6] a) J. B. Hendrickson, J. S. Farina, *J. Org. Chem.* **1980**, *45*, 3361; b) R. G. Arrayás, L. S. Liebeskind, *J. Am. Chem. Soc.* **2003**, *125*, 9026.

[7] a) E. O. M. Orlemans, B. H. M. Lammerink, F. C. J. M. V. Veggel, W. Verboom, S. Harkema, D. N. Reinhoudt, *J. Org. Chem.* **1988**, *53*, 2278; b) F. A. G. El-Essawy, S. M. Yassin, I. A. El-Sakka, A. F. Khattab, I. Søtofte, J. Ø. Madsen, A. Senning, *J. Org. Chem.* **1998**, *63*, 9840; c) D. Garayalde, C. Nevado, *ACS Catal.* **2012**, *2*, 1462.

[8] a) Y. Ueda, G. Roberge, V. Vinet, *Can. J. Chem.* **1984**, *62*, 2936; b) H. M. L. Davies, Z.-Q. Peng, J. H. Houser, *Tetrahedron Lett.* **1994**, *35*, 8939.

[9] a) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402; b) X. Xu, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2013**, *52*, 12664; *Angew. Chem.* **2013**, *125*, 12896; c) X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 12439.

[10] D. J. Lee, H. S. Han, J. Shin, E. J. Yoo, *J. Am. Chem. Soc.* **2014**, *136*, 11606.

[11] See the Supporting Information for details.

[12] Selected references for rhodium catalysts: a) N. Watanabe, T. Ogawa, Y. Ohtake, S. Ikegami, S. Hashimoto, *Synlett* **1996**, 85; b) H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, S. Hashimoto, *Org. Lett.* **2002**, *4*, 3887; c) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378; d) R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 3447; e) J. R. Denton, D. Sukumaran, H. M. L. Davies, *Org. Lett.* **2007**, *9*, 2625; f) A. DeAngelis, O. Dmitrenko, G. P. A. Yap, J. M. Fox, *J. Am. Chem. Soc.* **2009**, *131*, 7230; g) A. G. Smith, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 18241.

[13] Yield was presumably increased by the adsorption of nitrogen gas on the molecular sieve. H. Verelst, G. V. Baron, *J. Chem. Eng. Data* **1985**, *30*, 66.

[14] G. Song, D. Chen, Y. S. Han, C.-L. Pan, A. Jia, X. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 7791; *Angew. Chem.* **2011**, *123*, 7937.

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