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An Ylide Transformation of Rhodium(I) Carbene: Enantioselective Three-Component Reaction through Trapping of Rhodium(I)-Associated Ammonium Ylides by β-Nitroacrylates**

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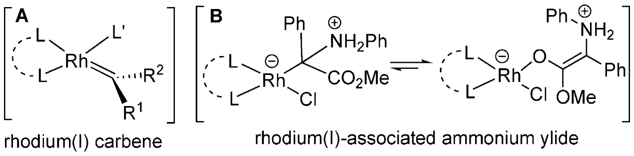
Dedicated to Professor Lixin Dai on the occasion of his 90th birthday

***Abstract:** The chiral Rh^I–diene-catalyzed asymmetric three-component reaction of aryldiazoacetates, aromatic amines, and β-nitroacrylates was achieved to obtain γ-nitro-α-amino-succinates in good yields and with high diastereo- and enantioselectivity. This reaction is proposed to proceed through the enantioselective trapping of Rh^I-associated ammonium ylides by nitroacrylates. This new transformation represents the first example of Rh^I-carbene-induced ylide transformation.*

Rhodium(I) complexes have been known as efficient catalysts for the hydrogenation of olefins.[1] In recent years, the application of rhodium(I) catalysts has been extended to 1) the intramolecular [3+2] cycloaddition of alkynes with vinylcyclopropane[2a] and the intermolecular [5+1][2b] and [5+2] cycloaddition[2c] of 1,4-enynes; and 2) the asymmetric addition of organoboronic acids to Michael acceptors.[3] In contrast, only limited examples of rhodium(I) carbene chemistry in which rhodium(I) complexes were employed to catalyze the decomposition of diazo compounds have been reported (Scheme 1 A). Demonceau[4] reported the first example of a Rh^I-catalyzed cyclopropanation of alkenes with ethyl diazoacetate; Hayashi and co-workers[5] developed an asymmetric version using dimethyl diazomalonate via rhodium(I) carbene intermediates. Recently, Wang and co-workers established a reaction of rhodium(I) carbene insertion into the C–C bond of benzocyclobutenols to construct indanol derivatives.[6] Herein, we report the first example of rhodium(I) carbene ylide chemistry. Rh^I-associated ammonium ylides (Scheme 1 B) are shown to react with nitroacrylates affording polyfunctionalized nitrogen-containing molecules in high diastereo- and enantioselectivity.



Scheme 1. Rhodium(I) carbene and ylide intermediates.

For decades, we are interested in the enantioselective trapping of active intermediates by electrophiles to provide rapid and highly efficient approaches to construct polyfunctional molecules.[7] The active intermediates including onium ylides and zwitterions are typically generated in situ from rhodium(II) carbene with molecules bearing heteroatom lone pair electrons, and the electrophilic trapping agents include imines, aldehydes, and α,β-unsaturated ketoesters.[8] Such an approach has also been investigated by other research groups; for example, the highly enantioselective trapping of ammonium ylides by carbonyl compounds has recently been reported by the groups of Che and Gong.[9] However, to the best of our knowledge, there are no examples of trapping these active intermediates by conjugated nitroolefins possibly due to the mismatch reactivity.

To promote the trapping of ammonium ylides by nitroolefins, nitroacrylate was selected as the representative trapping agent due to its good electrophilicity and rich functionality. The initial investigation was commenced by examining the three-component reaction of methyl phenyldiazoacetate (**1a**) and methyl anthranilate (**2a**)[9b] with isopropyl (*E*)-3-nitroacrylate (**3a**) using the commonly used catalysts for carbene generation[10] (see Table 1). When $Rh_2(OAc)_4$, Rh_2(S-NTTL)$_4$, $AgSbF_6$, $Hg(OTf)_2$, $Pd_2(dba)_3$, $AuCl_3$, and [Ru(*p*-cymene)Cl$_2$]$_2$[11] were used, less than 10% yield of the reaction product was obtained, but an N–H insertion side product and/or dimer from the diazo compound were observed (see the Supporting Information, SI). Then, commercially available rhodium(I) complexes, $[Rh(CO)_2Cl]_2$, [Rh(cod)Cl]$_2$, and $[Rh(C_2H_4)_2Cl]_2$ were investigated, expecting that their extraordinary additional coordination ability[12] would activate the nitroacrylate substrate. $[Rh(CO)_2Cl]_2$ decomposed **1a** very slowly (the conversion was approximately 10% after 24 h) and a trace amount of the desired product **4a** was obtained along with the major aza-Michael

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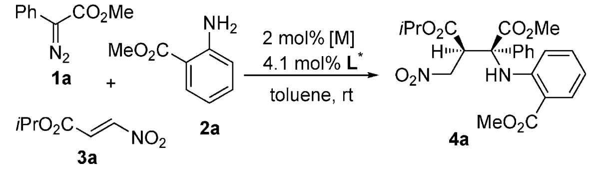
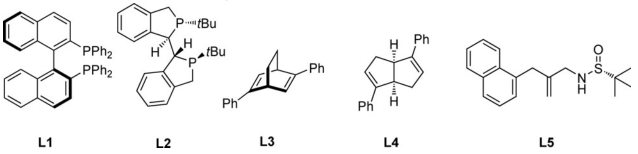
Table 1: Catalyst screening for the three-component reaction.[a]



Entry	[M]	L*	Yield[b] [%]	d.r.[c]	e.r.[d]
1	$[Rh(CO)_2Cl]_2$	–	trace	N.D.	N.D.
2	$[Rh(C_2H_4)_2Cl]_2$	–	N.P.	–	–
3	$[Rh(cod)Cl]_2$	–	58	88:12	N.D.
4	$[Rh(cod)Cl]_2$	**L1**	42	80:20	60:40
5	$[Rh(cod)Cl]_2$	**L2**	N.P.	–	–
6	$[Rh(cod)Cl]_2$	**L3**	53	82:18	51:49
7	$[Rh(CO)_2Cl]_2$	**L3**	trace	N.D.	N.D.
8	$[Rh(C_2H_4)_2Cl_2]_2$	**L3**	65	95:5	97:3
9	$[Rh(C_2H_4)_2Cl]_2$	**L4**	46	95:5	75:25
10	$[Rh(C_2H_4)_2Cl]_2$	**L5**	12	70:30	79:21
11	$[Rh(\mathbf{L3})Cl]_2$	–	62	95:5	96:4

[a] Unless otherwise noted, all reactions were carried out in toluene at room temperature in 0.05 mmol scale and **1a**/**2a**/**3a** = 1.1 : 1.1 : 1.0. 4 Å MS (100 mg) and 2 mol% metal catalyst, 4.1 mol% L* were added.
[b] The diastereomeric ratio was detected by ^{1}H NMR spectroscopy.
[c] Yields of isolated products were obtained after purification by column chromatography. [d] Determined by HPLC analysis. N.D.: not determined, N.P.: no desired product.



addition product obtained through the addition of **2a** to **3a** (Table 1, entry 1). $[Rh(C_2H_4)_2Cl]_2$ showed no catalytic activity for the diazo decomposition (Table 1, entry 2). Gratifyingly, $[Rh(cod)Cl]_2$ produced the desired product **4a** in 58% yield with an 88:12 d.r. (entry 3).

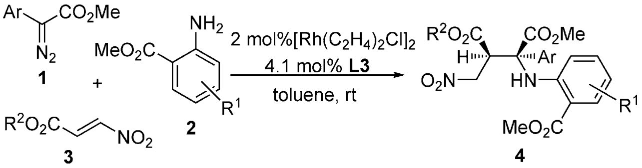
With these preliminary results, we focused on developing an asymmetric version of this transformation by introducing chiral ligands into the catalytic system. Chiral BINAP (**L1**) ligand[13] with $[Rh(cod)Cl]_2$ was found to be effective, but only induced a 60:40 e.r. with a slightly decreased d.r. (Table 1, entry 4). Other chiral phosphorus ligands such as DuanPhos **L2**[14] (entry 5) and (*R*)-DTBM-SEGPHOS showed negligible enantioselectivity (SI). Pioneered by the independent seminal works of the groups of Hayashi and Carreira, chiral dienes have shown excellent asymmetric induction in the Rh^I-catalyzed addition of organoboronic acids or organometallic reagents to electron-deficient olefins compared to the privileged phosphorus ligands.[15] Therefore, Hayashi's chiral diene ligand **L3** was investigated using different rhodium(I) precursors. However, both $[Rh(CO)_2Cl]_2$ and $[Rh(cod)Cl]_2$ gave no improvement in catalytic activity (entries 6 and 7), probably because of insufficient ligand exchange with the chiral diene. Intriguingly, $[Rh(C_2H_4)_2Cl]_2$ afforded **4a** in 65% yield and with 95:5 d.r. and 97:3 e.r. of the major diastereomer (entry 8). The chiral olefin ligands **L4**[16] and **L5**,[17] developed by the groups of Lin and Xu, respectively, were effective, but less efficient compared to ligand **L3** in this reaction (entries 9 and 10).

When the chiral complex, $[Rh(\mathbf{L3})Cl]_2$, was synthesized and employed in the reaction, comparable yield and the same *ee* value were obtained (Table 1, entry 11). This control experiment indicates that a ligand exchange occurred between chiral ligand **L3** and $[Rh(C_2H_4)_2Cl]_2$, forming an effective chiral Rh^I–diene catalyst. The significant effect of ligands on the ability of rhodium(I) complexes to decompose diazo compounds is still unclear; it is probably due to the different electronic nature of Rh^I influenced by various ligands. The present three-component reaction provides a rapid, atom-efficient, and step-economic method to construct polyfunctional γ-nitro-α-amino succinates, which are difficult to obtain in an optically active form by classical methods.[18]

The effects of solvent and reaction temperature on the reaction selectivity were investigated (SI), and the optimal conditions were established as follows: 2 mol% of $[Rh(C_2H_4)_2Cl]_2$ with 4.1 mol% of chiral ligand **L3** in toluene at room temperature with 4 Å MS as the additive (Table 1, entry 8).

Next, the substrate scope was investigated, and the results are shown in Table 2. The current reaction tolerates diverse substrates. An *ortho*-carbomethoxy group in the aromatic amine **2** was found to be preferable to achieve high diastereoselectivity in the current transformation (SI). An additional substituent, either electron-withdrawing or -donating, at the 4-position of the aromatic amine significantly improved the yield with a slightly decreased enantio- and diastereoselectivity (Table 2, entries 2 and 3). Both diazo compounds with electron-withdrawing and -donating groups on the phenyl ring afforded the corresponding products in moderate yields and with good d.r. and *ee* (entries 4–8). The substituents on the ester group of nitroacrylates had a large influence on the enantioselectivity of the reaction. For example, with the increase in the size of the substituent

Table 2: Scope of substrates.[a]



Entry	Ar	R^1	R^2	4	Yield[b] [%]	d.r.[c]	e.r.[d]
1	Ph	H	*i*Pr	**4a**	64	> 95:5	97:3
2	Ph	4-Cl	*i*Pr	**4b**	74	91:9	81:19
3	Ph	4,5-dimethoxy	*i*Pr	**4c**	85	91:9	90:10
4	*m*Cl-C_6H_4	4,5-dimethoxy	*i*Pr	**4d**	47	88:12	93:7
5	*m*Br-C_6H_4	4,5-dimethoxy	*i*Pr	**4e**	42	> 95:5	92:8
6	*p*Br-C_6H_4	H	*i*Pr	**4f**	48	> 95:5	92:8
7	*p*MeO-C_6H_4	H	*i*Pr	**4g**	60	91:9	94:6
8	*p*Me-C_6H_4	H	*i*Pr	**4h**	68	92:8	97:3
9	Ph	H	Et	**4i**	53	89:11	75:25
10	Ph	H	Bn	**4j**	67	86:14	73:27
11	Ph	H	Me	**4k**	72	92:8	92:8
12	Ph	H	*t*Bu	**4l**	45	86:14	88:12
13	Ph	4,5-dimethoxy	Me	**4m**	62	95:5	95:5

[a], [b], [c], [d] Reaction conditions as stated in Table 1.

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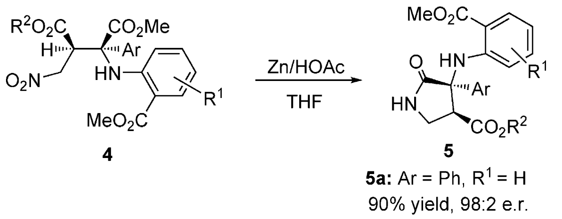
from a methyl to a *tert*-butyl group, both the product yield and stereoselectivity decreased (entry 12 versus 11).

The relative stereochemistry of **4b** was determined as *syn*-**4b** by the single-crystal X-ray analysis of racemic **4b** (SI), and the absolute configuration of the major enantiomer of *syn*-**4b** was deduced to be (2*R*,3*R*) by comparing its circular dichroism (CD) spectrum with that of a reference compound. The theoretically calculated electronic circular dichroism (ECD) spectrum is well consistent with the CD spectrum of *syn*-**4b** (SI). The stereochemistry of other products was tentatively assigned by analogy. Control reactions excluded the possibility that product **4a** was formed by the addition of an N−H insertion product (derived from **1a** to **2a**) to **3a**.

The synthetic applications of the three-component reaction products were illustrated by the simple reduction of the nitro group to the amine group, followed by an intramolecular ring closure to afford the corresponding 3-aminopyrrolidin-2-one derivatives. Optically active 3-aminopyrrolidinones serve as pivotal structural moieties in pharmaceutical research (Scheme 2).[19]



Scheme 2. Synthesis of 3-aminopyrrolidinone derivatives.

To identify how the Rh^I metal center associates with the ammonium ylide, theoretical calculations of the Gibbs free energy of the two possible ylide structures were conducted. The free energy of enolate form **IV** was ca. 14.9 kcal mol^{-1} lower than that of ylide form **III** (Figure 1), calculated with Gaussian 09 at the B3LYP level of theory using the lanl2dz basis set for Rh and the 6-31+G** basis set for other atoms.[20] This indicates that the enolate form **IV** is more stable than the ylide form **III**. Furthermore, the enolate form **IV** is proposed to activate nitroacrylate by the coordination of Rh^I with the C=C double bond. The theoretically calculated transition state **V** (SI) is proposed as one possibility to explain the observed absolute configuration of the major stereoisomer (Figure 2). In transition state **V**, an intimate ion pair with chloride is obtained, probably due to the solvent-assisted neutral-to-cationic switch.[21]

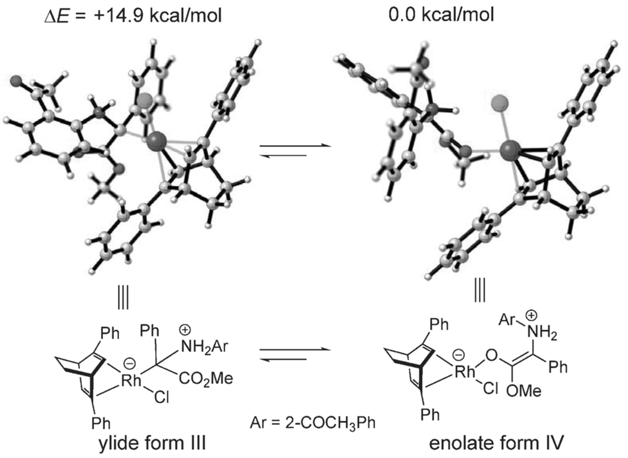


Figure 1. The theoretically computed Gibbs free energy of the enolate versus the ylide form.

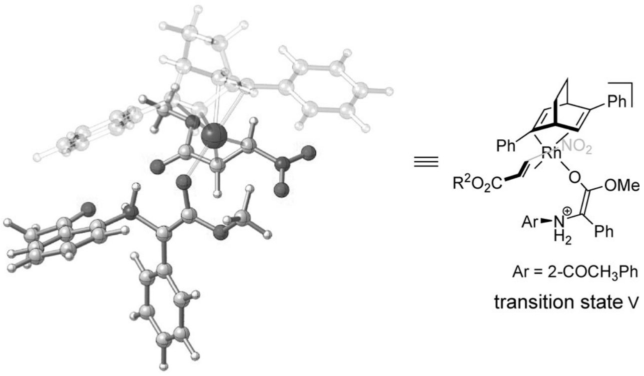
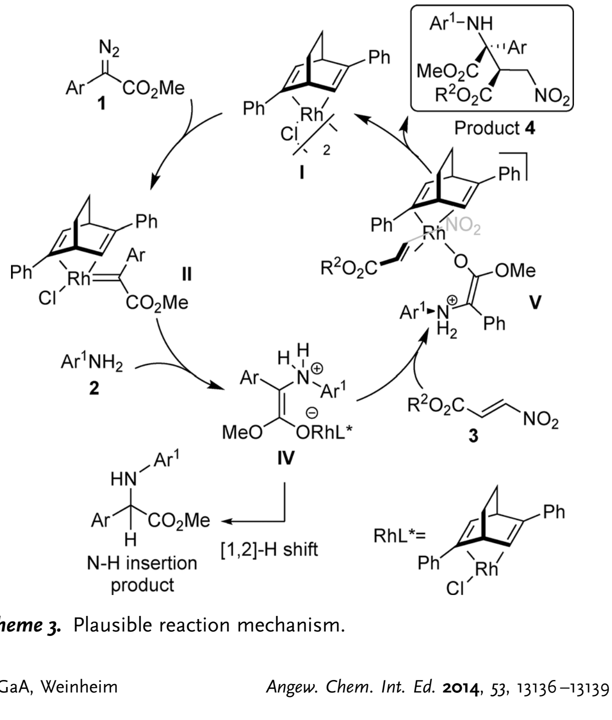


Figure 2. The theoretically calculated transition state **V**.

To gain further insight into the reaction mechanism, a solution of the reaction mixture was analyzed by HPLC-MS to monitor the progress of the reaction. The molecular ion peak of the chiral rhodium(I) complex **I** dimer ([Rh(**L3**)Cl]$_2$) was found to be 793.2 (calculated $[M+H]^+$ for **I** is 793.04) during the entire course of the reaction. Based on the results, a plausible reaction pathway is proposed (Scheme 3). First, the ligand exchange between [Rh(C$_2$H$_4$)$_2$Cl]$_2$ and chiral diene ligand **L3** generates chiral rhodium(I) complex dimer **I**. The dimer **I** is proposed to dissociate into the corresponding Rh^I–diene monomer, which decomposes diazo compound **1** to



Scheme 3. Plausible reaction mechanism.

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form Rh^I-associated carbene **II**. Subsequently, the nucleophilic attack by aromatic amine **2** generates the Rh^I-associated ylide intermediate, enolate **IV**. Finally, product **4** is obtained through the proposed transition state **V**, regenerating the Rh^I catalyst in its dimer form.

In conclusion, the Rh^I–chiral diene complex is an efficient catalyst to generate Rh^I-associated ammonium ylides from aryldiazoacetates and anilines. The ammonium ylides exhibited unique reactivity and underwent reaction with nitroacrylates in a Michael addition-type fashion. The present enantioselective three-component reaction provides a mild, atom-efficient, and step-economic method to synthesize polyfunctional amino succinic acid derivatives in good yields and with high diastereo- and enantioselectivity. This study extends the application of versatile Rh^I–diene complexes as the efficient chiral catalysts in asymmetric transformation and enriches rhodium(I) carbene chemistry. The applications of rhodium(I) complexes with chiral dienes or other chiral ligands in carbene ylide chemistry are currently investigated in our laboratory.

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[1] a) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998; *Angew. Chem.* **2002**, *114*, 2096, and references therein; b) P. Etayo, A. V. Ferran, *Chem. Soc. Rev.* **2013**, *42*, 728.

[2] a) M. Lin, G.-Y. Kang, Y. A. Guo, Z.-X. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 398; b) X.-X. Li, W.-Z. Song, W.-P. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 16797; c) X.-F. Xu, P. Liu, X.-Z. Shu, W.-P. Tang, K. N. Houk, *J. Am. Chem. Soc.* **2013**, *135*, 9271.

[3] a) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; b) T. Nishimura, A. Noishiki, G. C. Tsui, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 5056; c) H. Wang, T. Jiang, M. H. Xu, *J. Am. Chem. Soc.* **2013**, *135*, 971; d) T. Nishimura, Y. Takiguchi, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 9086; e) Z.-Q. Wang, C.-G. Feng, M.-H. Xu, G.-Q. Lin, *J. Am. Chem. Soc.* **2007**, *129*, 5336.

[4] A. Demonceau, F. Simal, A. F. Noels, *Tetrahedron Lett.* **1997**, *38*, 7879.

[5] T. Nishimura, Y. Maeda, T. Hayshi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7324; *Angew. Chem.* **2010**, *122*, 7482.

[6] Y. Xia, Z.-X. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang, J.-B. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 3013.

[7] X. Guo, W.-H. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427.

[8] For asymmetric reactions involving ammonium ylides: a) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, G. Xin, L.-Q. Jiang, Z.-Y. Zhang, W.-H. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428; b) J. Jiang, X.-C. Ma, S.-Y. Liu, Y. Qian, F.-P. Lv, L. Qiu, X. Wu, W.-H. Hu, *Chem. Commun.* **2013**, *49*, 4238; c) L.-Q. Jiang, D. Zhang, Z.-Q. Wang, W.-H. Hu, *Synthesis* **2013**, 452. For asymmetric reactions involving oxonium ylides: d) W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.-X. Huang, J. Hu, L.-P. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782; e) Y. Qian, X.-F. Xu, L.-Q. Jiang, D. Prajapati, W.-H. Hu, *J. Org. Chem.* **2010**, *75*, 7483; f) X.-Y. Guan, L.-P. Yang, W.-H. Hu, *Angew. Chem. Int. Ed.* **2010**, *49*, 2190; *Angew. Chem.* **2010**, *122*, 2236; g) Y. Qian, C.-C. Jing, T.-D. Shi, J.-J. Ji, M. Tang, J. Zhou, C.-W. Zhai, W.-H. Hu, *ChemCatChem* **2011**, *3*, 653. For asymmetric reactions involving zwitterionic intermediates: h) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nat. Chem.* **2012**, *4*, 733; i) D. Zhang, H. Qiu, L.-Q. Jiang, F.-P. Lv, C.-Q. Ma, W.-H. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13356; *Angew. Chem.* **2013**, *125*, 13598; j) H. Qiu, D. Zhang, S. Y. Liu, L. Qiu, J. Zhou, Y. Qian, C. W. Zhai, W.-H. Hu, *Acta Chim. Sin.* **2012**, *70*, 2484.

[9] a) C.-Y. Zhou, J.-C. Wang, J.-H. Wei, Z.-J. Xu, Z. Guo, K.-H. Low, C.-M. Che, *Angew. Chem. Int. Ed.* **2012**, *51*, 11376; *Angew. Chem.* **2012**, *124*, 11538; b) L. Ren, X.-L. Lian, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 3315.

[10] M. P. Doyle, M. A. Mckervery, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.

[11] a) E. Galardon, P. L. Maux, G. Simonneaux, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2455; b) E. Galardon, P. L. Maux, G. Simonneaux, *Tetrahedron* **2000**, *56*, 615; c) A. Del Zotto, W. Baratta, P. Rigo, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3079; d) Q.-H. Deng, H.-W. Xu, A. W. H. Yuen, Z.-J. Xu, C.-M. Che, *Org. Lett.* **2008**, *10*, 1529; e) J. Jiang, X.-C. Ma, C.-G. Ji, Z.-Q. Guo, T.-D. Shi, S.-Y. Liu, W.-H. Hu, *Chem. Eur. J.* **2014**, *20*, 1505.

[12] P. A. Evans, J. Tsuji, *Modern Rhodium-Catalyzed Organic Reactions*, Wiley-VCH, Weinheim, **2005**, pp. 55–76.

[13] A. Börner, *Phosphorus Ligands in Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2008**.

[14] D. Liu, X.-M. Zhang, *Eur. J. Org. Chem.* **2005**, 646.

[15] a) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508; b) C. Defieber, J. F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873.

[16] a) C.-G. Feng, M.-H. Xu, G.-Q. Lin, *Synlett* **2011**, 1345; b) Z. Cui, Y. J. Chen, W. Y. Gao, C. G. Feng, G. Q. Lin, *Org. Lett.* **2014**, *16*, 1016.

[17] S.-S. Jin, H. Wang, T.-S. Zhu, M.-H. Xu, *Org. Biomol. Chem.* **2013**, *10*, 1764.

[18] a) T. Ooi, M. Kameda, J. Fuji, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397; b) K. R. Knudsen, K. A. Jorgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362; c) A. Puglisi, L. Raimondi, M. Benaglia, M. Bonsignore, S. Rossi, *Tetrahedron Lett.* **2009**, *50*, 4340.

[19] a) P. D. Leeson, B. J. Williams, M. Rowley, K. W. Moore, R. Baker, J. A. Kemp, T. Priestley, A. C. Foster, A. E. Donald, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 71; b) Y. Vo-Hoang, C. Gasse, M. Vidal, C. Garbay, H. Galons, *Tetrahedron Lett.* **2004**, *45*, 3603.

[20] M. J. Frisch et al. Gaussian09, Rev.B.01; Gaussian, Inc., Wallingford, **2010**.

[21] C. C. C. Seechurn, V. Sivakumar, D. Satoskar, T. J. Colacot, *Organometallics* **2014**, *33*, 3514.

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