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Titanium-mediated cross-coupling reactions of imines with ketones or aldehydes: an efficient route for the synthesis of 1,2-amino alcohols

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ABSTRACT

The cross-coupling reactions of imines with ketones using $Ti(O^iPr)_4/c\text{-}C_5H_9MgCl$ reagent lead to 1,2-amino alcohols after hydrolysis. The coupling reactions with aldehydes could also afford 1,2-amino alcohols, however, in some cases, aziridines were obtained as major products in a stereoselective manner.

Group 4 metallacyclic compounds, such as titana- or zirconacycles, are attractive intermediates in organic synthesis, which have received considerable attention during the past several decades.[1] These metallacycles can be easily prepared by the reductive coupling of unsaturated compounds such as alkynes, alkenes, nitriles, ketones etc. on a low-valent metal equivalent. They are relatively stable under certain reaction conditions, however, upon treatment with suitable electrophiles, they can display diverse reactivities leading to a wide range of selective transformation reactions.[2] Although much progress has been achieved in this chemistry, most of the studies concentrated on the metallacycles synthesized via coupling reactions of two unsaturated molecules in which at least one of the component is alkyne or alkene. There are only limited reports for the preparation of heterometallacycles via coupling reactions of two heteroatom-substituted π-systems such as aldehydes, ketones, nitriles, imines, and so on. For example, cross-coupling reactions of imines and aldehydes can be achieved via reactions of carbonyl compounds with a metal complex of imines.[3,4] These reactions could provide a useful route for the synthesis of 1,2-amino alcohol derivatives, which are widely used as important building blocks for the synthesis of biologically active targets, and as ligands for asymmetric synthesis.[5] Buchwald et al. reported that zirconocene-imine complexes, generated by treating $Cp_2ZrMeCl$ with lithium dialkylamide followed by elimination of methane from the resulting zirconocene(methyl) amide complex, coupled with aldehydes in a diastereoselective fashion to give metallacyclic products.[3] Taguchi and co-workers also described Cp_2ZrBu_2-mediated coupling reactions of chiral aldimines with aldehydes.[4] However, these reactions either require the tedious multi-step synthesis or restricted to special substituted imines. In contrast, titanium-imine complex prepared via activation of imines with $Ti(O^iPr)_4/^iPrMgCl$ system do not lead to the expected coupling products with aldehydes,[6] and there is also no report for titanium-mediated coupling reactions of imines with ketones, to the best of our knowledge. Recently, we have developed a series of reactions on utilization of low-valent titanium reagents,[7] including selective coupling of 1,3-butadiynes with aldehydes using $Ti(O^iPr)_4$/n-BuLi reagent[7a] and titanium-mediated *cis*-[3]cumulenes formation in the presence of Lewis acid.[7b] These results prompted us to examine the synthetic route for the formation of heterometallacycles. We now report an efficient imine/ketone or aldehyde coupling reactions using $Ti(O^iPr)_4/c\text{-}C_5H_9MgCl$ reagent.

We began our investigation of titanium-mediated coupling reactions of imines with ketones. It occurred to us that to achieve the desired coupling reactions, the proper choice of the Grignard reagent for producing the low valent Ti^{II}-equivalent is very important. After a lot of efforts, we found that Ti-imine complex **2** (can be elucidated as azatitanacyclopropane) generated by reactions of imine with $Ti(O^iPr)_4/c\text{-}C_5H_9MgCl$[8] at −30 °C could couple with ketones smoothly (Scheme of Table 1). The procedure is operationally convenient: To a solution of imine **1a** and 1.3 equiv of $Ti(O^iPr)_4$ in Et_2O at −30 °C was added 2.6 equiv of $c\text{-}C_5H_9MgCl$, the mixture was stirred at the same temperature for 1.5 h. Quenching the mixture at this stage by D_2O followed by aqueous workup afforded the reduction product PhCH(D)NHPh in 98% yield with a deuterium

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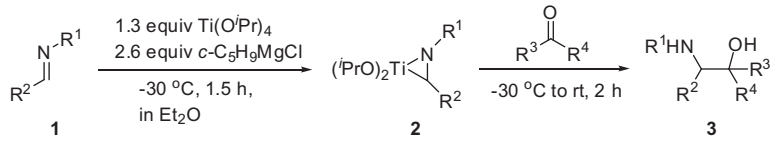
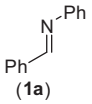
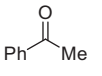
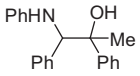
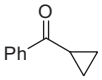
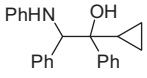
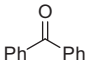
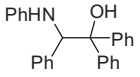
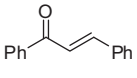
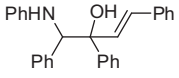
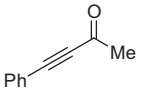
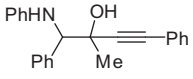
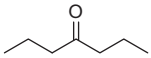
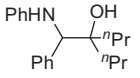
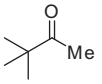
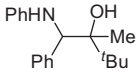
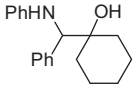
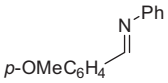
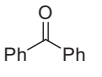
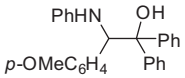
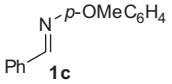
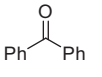
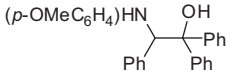
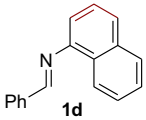
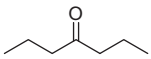
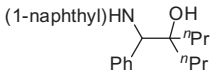
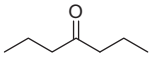
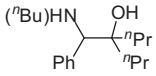
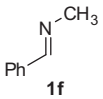
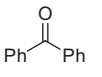
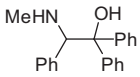
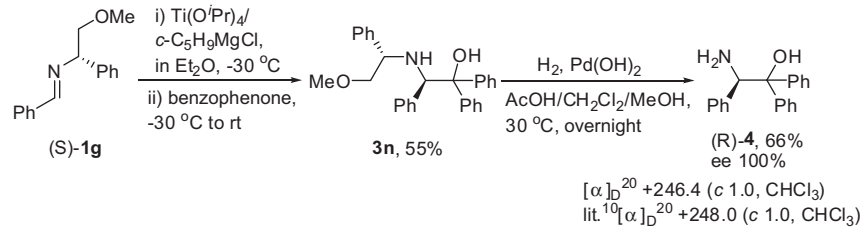
Table 1
Titanium-mediated coupling reactions of imines with ketones



Entry	Imine	Ketone	Product		Yield[a] (%)
1	 (**1a**)			**3a**	88 (2:1)
2	**1a**			**3b**	82 (4.3:1)
3	**1a**			**3c**	80
4	**1a**			**3d**	80 (3:1)
5	**1a**			**3e**	62 (1.6:1)
6	**1a**			**3f**	79
7	**1a**			**3g**	83[b]
8	**1a**			**3h**	47
9	 **1b**			**3i**	81
10	 **1c**			**3j**	74
11	 **1d**			**3k**	64
12	 **1e**			**3l**	71
13	 **1f**			**3m**	61

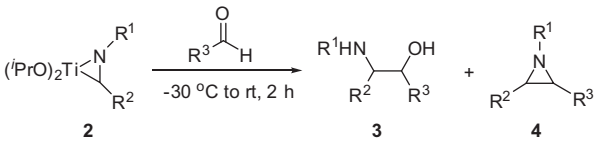
[a] Isolated yields. 1.2 equiv of ketone were used. Diastereomeric ratios are shown in the parentheses, which were determined by ^{1}H NMR.
[b] **3g** was obtained as a single diastereomer, the stereochemistry was not defined yet.

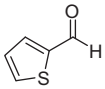
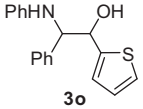
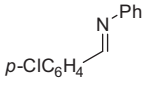
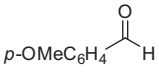
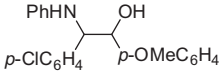
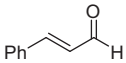
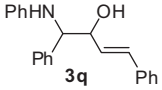
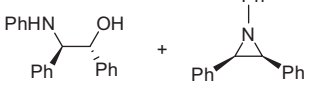
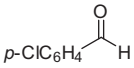
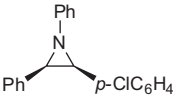
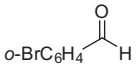
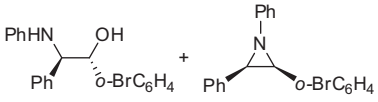
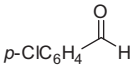
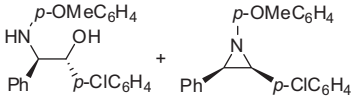
incorporation of 96%. The results strongly indicated the formation of azatitanacyclopropane **2a**. Addition of acetophenone instead of hydrolysis followed by warming up to room temperature provided, after aqueous workup, the 1,2-amino alcohol **3a** in 88% yield as a mixture of two diastereomers (Table 1, entry 1). With the optimized reaction conditions in hand, we next examined the reaction scope with respect to various imines and ketones. As shown in Table 1, the reactions worked well with aryl or dialkyl ketones. Aryl ketones substituted with alkyl, aryl, alkenyl, or alkynyl groups were all compatible for coupling reactions, furnishing the corresponding products in generally good yields (entries 1–5, 9–10, and 13). The functionalities of cyclopropyl, alkenyl, and alkynyl moieties were well tolerated during the reaction. Sterically demanding ketones such as benzophenone and 3,3-dimethylbutan-2-one also coupled with imines to afford the desired products in 61–83% yields (entries 3, 7, 9–10, and 13). As for imines, *N*-aryl



Scheme 1. Chiral induction via coupling reaction of chiral aldimine with ketone.

Table 2
Titanium-mediated coupling reactions of imines with aldehydes



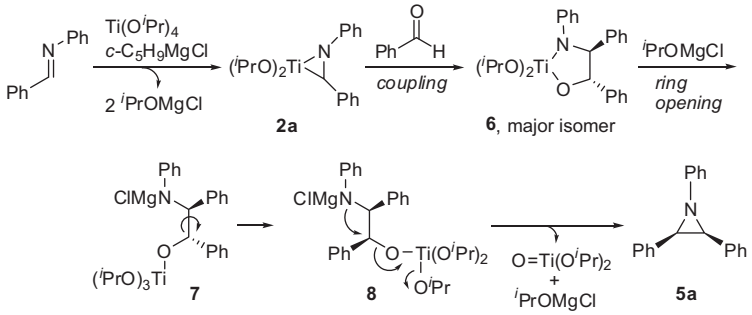
Entry	Imine	Aldehyde	Product	Yield[a]
1[b]	 **1a**		 **3o**	61% (9.1:1)
2[b]	 **1h**		 **3p**	72% (6.7:1)
3[b]	**1a**		 **3q**	59% (2.4:1)
4[c]	**1a**		 **3r**,[d] 18% (33:1) **5a**, 53%	
5[c]	**1a**		 **5b**, 60%	
6[b]	**1a**		 **3s**, 9% **5c**, 41%	
7[b]	**1c**		 **3t**, 11% **5d**, 32%	

[a] Isolated yields. Diastereomeric ratios are shown in the parentheses, which were determined by ^{1}H NMR.
[b] 1.2 equiv of aldehyde were used.
[c] 1.0 equiv of aldehyde was used.
[d] Stereochemistry of the major isomer of **3r** is shown as indicated.

and *N*-alkyl imines all could be used in this reaction, showing a broad range of imine substrates.

Interestingly, the coupling reaction of the chiral imine (S)-**1g**[4,8c9] with benzophenone gave the product **3n** in 55% yield as a single diastereomer (Scheme 1). The stereochemistry of **3n** was determined by conversion of **3n** into the corresponding free 1,2-amino alcohol **4** by removal of the –CH(Ph)CH$_2$OMe group. The optically pure (R)-**4**[10] was obtained in 66% yield with 100% ee.

Next, we proceeded to examine the reactions with aldehydes. It was found that the reactions of imines with electron-rich aryl aldehydes such as 2-thiophenecarboxaldehyde and 4-methoxybenzaldehyde afforded the 1,2-amino alcohols **3o** and **3p** in 61%



Scheme 2. Possible reaction mechanism for the formation of *cis*-aziridines.

and 72% yields, respectively, with good diastereoselectivity (Table 2, entries 1 and 2). The reaction with cinnamaldehyde also afforded amino alcohol **3q** as a major product, however, with lower stereoselectivity (entry 3). Interestingly, the use of benzaldehyde resulted in the formation of aziridine **5a** as a major product, along with 18% of amino alcohol **3r** (entry 4). The stereochemistry of the major isomer of **3r** is *anti* with respect to two phenyl groups by comparing the NMR spectra with that of a known compound.[11] However, the stereochemistry of aziridine **5a** was found to be *cis* as confirmed by X-ray crystal analysis,[12] indicating that the configuration of hydroxyl-bearing carbon was inversed during the cyclization process. When electron-poor aryl aldehydes such as *p*-chloro- or *o*-bromobenzaldehydes were employed as coupling partners, aziridines **5b–5d** were also obtained as major products as a single diastereomer (entries 5–7). The *cis*-stereochemistry of **5b** was also verified by X-ray crystal analysis.[12] The configurations of **5c–5d** were deduced from that of **5a** and **5b**.

Although the detailed mechanism for the formation of aziridines is not clear yet, we tentatively propose the following pathway (Scheme 2): Insertion of a carbonyl group to azatitanacyclopentane **2a** affords hetero-substituted titanacycle **6**. As indicated by hydrolysis results, the two phenyl groups in **6** orient *trans* in the major isomer in order to avoid the steric hindrance. Ring-opening of **6** by ^{i}PrOMgCl produced by reactions of Ti(O^{i}Pr)$_4$ and c-C$_5$H$_9$MgCl occurs to deliver a linear complex **7**.[13] Attack of nitrogen nucleophile to the adjacent carbon from the backside of the oxygen leaving group provides the ring-closure product *cis*-aziridine **5a**.

In conclusion, we have developed an efficient method for the cross coupling reactions of imines with ketones or aldehydes using Ti(O^{i}Pr)$_4$/c-C$_5$H$_9$MgCl reagent. The present methodology is convenient and practical for the synthesis of 1,2-amino alcohols. In addition, the coupling reactions with benzaldehyde or electron-poor aryl aldehydes afford aziridines as major products in a stereoselective manner. Further studies on the scope and limitations of this method are currently in progress.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.020.

References and notes

1. (a) *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; (b) Takahashi, T.; Kanno, K. Metallocene in Regio- and Stereoselective Synthesis In *Topics in Organometallic Chemistry*; Takahashi, T., Ed.; Springer: Berlin, 2005; Vol. 8, p 217; (c) Zhang, W.; Zhang, S.; Xi, Z. *Acc. Chem. Res.* **2011**, *44*, 541; (d) Wolan, A.; Six, Y. *Tetrahedron* **2010**, *66*, 15; (e) Wolan, A.; Six, Y. *Tetrahedron* **2010**, *66*, 3097; (f) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.
2. For recent papers, see: For Ti: (a) Song, Z.; Hsieh, Y.; Kanno, K.; Nakajima, K.; Takahashi, T. *Organometallics* **2011**, *30*, 844; (b) Yatsumonji, Y.; Sugita, T.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2010**, *12*, 1968; (c) Hanamoto, T.; Yamada, K. *J. Org. Chem.* **2009**, *74*, 7559; (d) Lysenko, I. L.; Kim, K.; Lee, H. G.; Cha, J. K. *J. Am. Chem. Soc.* **2008**, *130*, 15997; (e) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1440; (f) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112; (g) Takahashi, T.; Song, Z.; Sato, K.; Kuzuba, Y.; Nakajima, K.; Kanno, K. *J. Am. Chem. Soc.* **2007**, *129*, 11678; (h) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764; (i) Takahashi, T.; Kuzuba, Y.; Kong, F.; Nakajima, K.; Xi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 17188; (j) Urabe, H.; Mitsui, K.; Ohta, S.; Sato, F. *J. Am. Chem. Soc.* **2003**, *125*, 6074; For Zr: (k) Fu, X.; Yu, S.; Fan, G.; Liu, Y.; Li, Y. *Organometallics* **2012**, *31*, 531; (l) Zhao, J.; Zhang, S.; Zhang, W.; Xi, Z. *Organometallics* **2011**, *30*, 3464; (m) Zhang, S.; Zhao, J.; Zhang, W.; Xi, Z. *Org. Lett.* **2011**, *13*, 1626; (n) Zhang, S.; Zhang, W. –X.; Zhao, J.; Xi, Z. *Chem. Eur. J.* **2011**, *17*, 2442; (o) Zhou, Y.; Wang, Y.; Xi, C. *Organometallics* **2011**, *30*, 5077; (p) Fu, X.; Liu, Y.; Li, Y. *Organometallics* **2010**, *29*, 3012; (q) Luo, Q.; Wang, C.; Gu, L.; Zhang, W. –X.; Xi, Z. *Chem. Asian J.* **2010**, *5*, 1120; (r) Zhang, S.; Sun, X.; Zhang, W. –X.; Xi, Z. *Chem. Eur. J.* **2009**, *15*, 12608; (s) Zhang, W. –X.; Zhang, S.; Sun, X.; Nishiura, M.; Hou, Z.; Xi, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 7227; (t) Li, S.; Qu, H.; Zhou, L.; Kanno, K.; Guo, Q.; Shen, B.; Takahashi, T. *Org. Lett.* **2009**, *11*, 3318; (u) Ni, Y.; Nakajima, K.; Kanno, K.; Takahashi, T. *Org. Lett.* **2009**, *11*, 3702; (v) Fu, X.; Chen, J.; Li, G.; Liu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5500; (w) Zhang, H.; Fu, X.; Chen, J.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 9351.
3. Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486.
4. Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469.
5. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b)*Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds., 1st ed.; Springer: Berlin, 1999.
6. Gao, Y.; Yoshida, Y.; Sato, F. *Synlett* **1997**, 1353.
7. (a) Chen, J.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 6655; (b) Chen, J.; Liu, Y. *Organometallics* **2010**, *29*, 505.
8. (a) Lecornué, F.; Ollivier, J. *Chem. Commun.* **2003**, 584; (b) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514; (c) Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Umenmura, S.; Micalizio, G. C. *J. Org. Chem.* **2010**, *75*, 8048.
9. Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 2145.
10. Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.
11. Kureshy, R. I.; Prathap, K. J.; Agrawal, S.; Khan, N. H.; Abdi, S. H. R.; Jasra, R. V. *Eur. J. Org. Chem.* **2008**, 3118.
12. See Supplementary data
13. For ligand exchange reactions of titanium complexes with lithium or sodium alkoxides, see Ref. 8b,c.