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# Stereochemical lability of azatitanacyclopropanes: dynamic kinetic resolution in reductive cross-coupling reactions with allylic alcohols† ‡

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**Azatitanacyclopropanes (titanaziridines) are shown to be stereochemically labile under reaction conditions for reductive cross-coupling. This fundamental property has been employed to realize highly selective asymmetric coupling reactions with allylic alcohols that proceed by dynamic kinetic resolution.**

While the history associated with metallacycle-mediated cross-coupling is rich, dating back nearly 70 years ago to the work of Reppe,[1] the broad synthetic utility of reactions that proceed under this mechanistic paradigm is becoming ever more apparent with recent contributions.[2] Modern advances have greatly increased substrate scope and have had a substantial impact on the manner in which this type of reactivity is achieved. For example, inexpensive and easy to handle metal alkoxides [Ti(Oi-Pr)$_4$] have been identified as reagent precursors to low-valent species capable of forming metal–π complexes under reaction conditions that are readily achieved outside of a glove box,[3] and new strategies for reaction design have emerged that offer fine control over reactivity and selectivity in intermolecular cross-coupling reactions between metal–π complexes and substituted alkenes, alkynes, and allenes.[4] Building on such advances, recent contributions have included the realization of Ti-mediated reductive cross-coupling reactions between metal–imine complexes and allylic alcohols (Fig. 1A, eqn (1)) – a reaction process that delivers complex homoallylic amines with control of allylic and homoallylic stereochemistry while establishing the geometry of di- and tri-substituted alkenes during the course of intermolecular C–C bond formation.[5] Reports have described the utility of this process in stereoselective synthesis and a general strategy to accomplish simple kinetic resolution of racemic Ti–imine complexes has been employed to render such coupling processes asymmetric (Fig. 1A, eqn (2)).[5a–c,6] Here, we report that the intermediate organometallic complex in this class of reductive cross-coupling undergoes rapid and reversible stereochemical isomerization under the reaction conditions, and that this behaviour can be employed to realize highly stereoselective coupling reactions en route to chiral homoallylic amines that proceed by dynamic kinetic resolution (Fig. 1B).

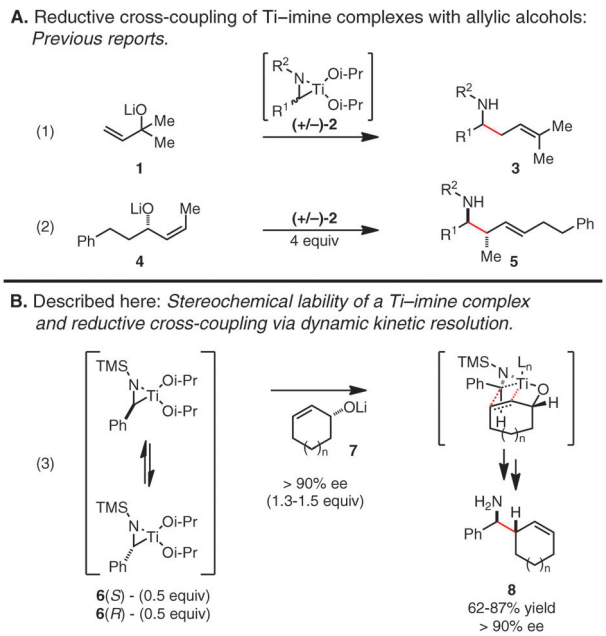


**Fig. 1** Reductive coupling of Ti–imine complexes with allylic alcohols: stereochemical lability of the complex and development of a dynamic kinetic resolution en route to homoallylic amines.

Since Kulinkovich's early reports that described the generation of vicinal dianion equivalents from the reaction of Ti(Oi-Pr)$_4$ with Grignard reagents, many new C–C bond-forming reactions have emerged that take advantage of the organometallic intermediates presumed to play a central role in this chemistry.[3] These processes have been presumed to proceed by the intermediacy of titanacyclopropanes, yet structural work to support this claim remains to be described (unlike related chemistry associated with Cp$_2$Ti- and

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† The authors dedicate this contribution in honor of Ruluan Gao for his lifetime contributions to the education of young students at Funing Middle School in Jiangsu, China – Dr Dexi Yang had the great pleasure of being inspired by the early chemistry teachings of Mr Gao.

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$Cp_2Zr$-based systems). In the subset of reactions most relevant to the current study, exposure of an imine to the reagent combination of $Ti(Oi\text{-}Pr)_4$–2RMgX or $Ti(Oi\text{-}Pr)_4$–2RLi is presumed to generate azatitanacyclopropanes (or titanaaziridines; *i.e.* **2**, Fig. 1A) and subsequent addition of an alkene, alkyne, or allene results in C–C bond formation by intermolecular carbometalation.[7] Titanaaziridines proposed to play a role in these processes have not been structurally characterized, yet gross reactivity patterns are consistent with their proposed intermediacy.

Cognizant of the uncertainty associated with the nature of the reactive organometallic species in $Ti(Oi\text{-}Pr)_4$–2RMet-promoted reactions of imines, we began an investigation aimed at exploring the configurational stability of the presumed titanaaziridine intermediates. Our first pursuit was designed to investigate whether a racemic mixture of titanaaziridines could be resolved in a manner to deliver an optically active organometallic complex for use in a subsequent stereoselective coupling reaction. A reaction scheme with this goal in mind is depicted in Fig. 2 (eqn (4)). Treatment of the TMS–imine **9**[8] with $Ti(Oi\text{-}Pr)_4$–2*c*-$C_5H_9MgCl$ was thought to result in the formation of a racemic mixture of azatitanacyclopropanes **6** [depicted as **6**(*R*) and **6**(*S*)]. Given our previous success in attaining high levels of stereoselection in reductive cross-coupling reactions with cyclic allylic alcohols, we added a single equivalent of the terpene-derived chiral allylic alkoxide **10** to the mixture of enantiomeric Ti–imine complexes **6** to achieve selective engagement of **6**(*S*) in reductive cross-coupling en route to **11**. In this manner, **6**(*S*) would be selectively removed from the reaction mixture leaving the resolved azametallacyclopropane **6**(*R*) available for a distinct stereoselective coupling process. Moving on, one equivalent of benzophenone was added to engage **6**(*R*) in a metallacycle-mediated coupling reaction en route to oxazametallacyclopentane **12**. Finally, addition of water resulted in the formation of the two chiral products: homoallylic amine **13** (62% from **10**; dr $\geq$ 20 : 1) and aminoalcohol **14** (81% from benzophenone). On further analysis of the aminoalcohol product, **14** *was found to be racemic* – an observation that supports the conclusion that the organometallic intermediate **6**(*R*) undergoes rapid and reversible stereochemical equilibration under the reaction conditions for reductive cross-coupling.

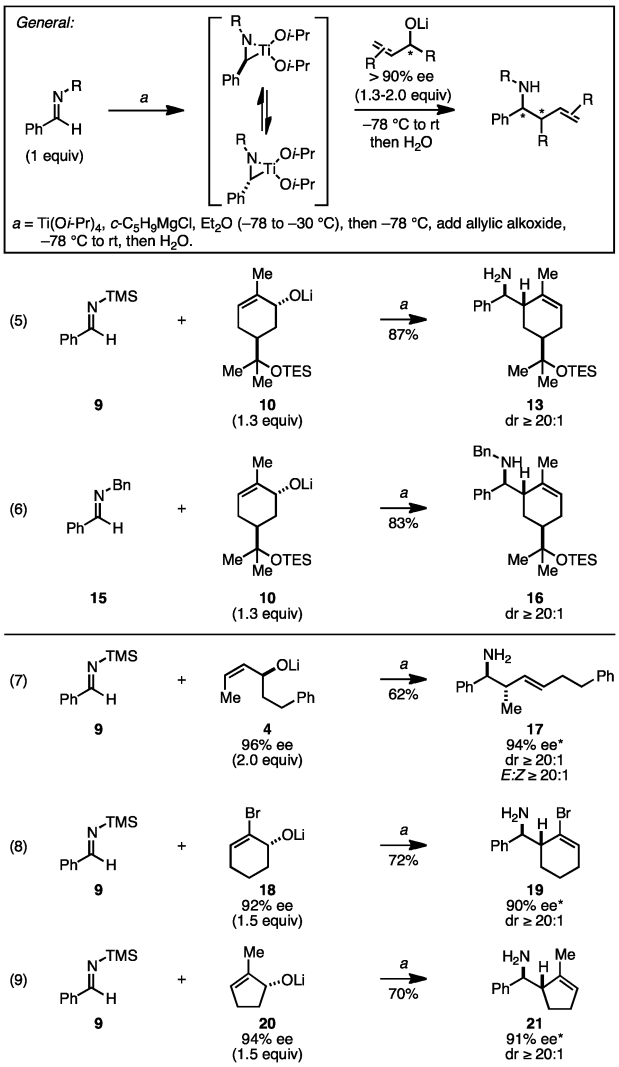


**Fig. 3** Dynamic kinetic resolution in reductive cross-coupling reactions of titanium–imine complexes with allylic alcohols. * = ee determined by $^1$H NMR analysis of the (+)-MTPA amide.

Recognizing that such stereochemical lability may be a useful property in the design of new reactions that proceed by

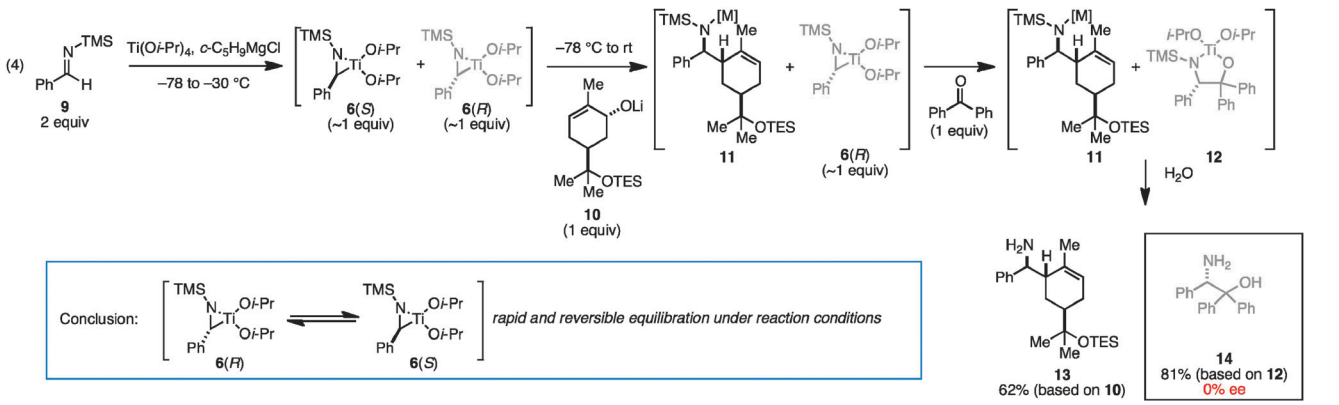


**Fig. 2** Observing the dynamic stereochemical behaviour of a presumed azatitanacyclopropane intermediate. Note: equivalents depicted below each reactive intermediate are estimates based on assuming complete conversion of **9** to **6** (*R* and *S*), and conversion of **6**(*S*) to **11**.

 

dynamic kinetic resolution (DKR), we explored the reductive cross-coupling of achiral aromatic imines with suitably substituted chiral allylic alcohols. As illustrated at the top of Fig. 3, conversion of one equivalent of an imine to a presumed equilibrating mixture of titanaaziridines was followed by addition of an excess of a chiral allylic alkoxide (1.3–2.0 equivalents) to consume as much of the equilibrating mixture as possible. Aqueous work up then delivered stereodefined homoallylic amine products. In all cases, these reductive cross-coupling reactions proceeded with exceptional levels of stereochemical control and in up to 87% yield – an efficiency that is based on the imine and due to the dynamic stereochemical behaviour of the organometallic intermediate.

From a synthetic perspective, we note that this DKR is compatible with a range of substrates that include TMS- and Bn-substituted aromatic imines (eqn (5) and (6)), as well as coupling partners harbouring cyclic and acyclic allylic alcohols, di- and trisubstituted alkenes, as well as vinyl bromides (eqn (7)–(9)).

While dynamic kinetic resolution of $Cp_2Zr$–imine complexes has been studied by Tunge and Norton and employed as a strategy to prepare chiral α-amino acids,[9] to our knowledge these studies describe the first observations consistent with stereochemical lability of titanaaziridine intermediates derived from $Ti(Oi\text{-}Pr)_4$, the first dynamic kinetic resolution of metal–imine complexes derived from Ti(IV)–alkoxides,[6,10,11] and establish a convenient method for the convergent asymmetric synthesis of highly substituted chiral homoallylic amines. Notably, the facile stereochemical isomerization of the organometallic intermediate observed here should prove useful for asymmetric metallacycle-mediated cross-coupling reactions of precious imines, where readily accessible chiral allylic alcohols can be used to dictate the absolute stereochemical course of C–C bond-formation.[12]

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10 The conclusions made from this study assume the intermediacy of racemic Ti–imine complexes similar to that which has been observed in related chemistry of $Cp_2Zr$–imine complexes (see ref. 9). The mechanism for interconversion between these presumed chiral intermediates may include that based on radical homolysis of the $\sigma_{Ti-C}$ bond and subsequent reformation of the metallacycle. Such a mechanism would imply that aryl imines would be superior substrates to aliphatic imines in this DKR due to an enhanced stability of the resulting benzylic radical. While not presented in the body of the current manuscript, we have explored the potential utility of aliphatic imines in this resolution process. Unfortunately, when an aliphatic imine is employed as limiting reagent, we have not been able to achieve yields of the homoallylic amine product over 25%. The reasons associated with the divergent efficiency of this process could be related to a number of factors that include the different reaction conditions required for aliphatic imines (see ref. 7*b*) and the stability of radical intermediates derived from homolysis of the $\sigma_{Ti-C}$ bond of the presumed titanaaziridne intermediate.

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12 The current contribution is of great synthetic value when the cost of the imine far outweighs the cost of the allylic alcohol, as 1.3–2 equivalents of the chiral allylic alcohol are employed to engage the Ti–imine complex in an efficient dynamic kinetic resolution. In cases where the chiral allylic alcohol is significantly more expensive than the imine coupling partner, potential users of this imine–allylic alcohol coupling process should purse simple kinetic resolution using the allylic alcohol coupling partner as limiting reagent. Such a procedure has been described earlier (see ref. 5).