Concerning the Potential Reversibility of Carbometalation in Alkoxide-directed Ti(O*i*-Pr)₄-mediated Reductive Cross-Coupling of Homoallylic Alcohols with Aromatic Imines

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Abstract

In an attempt to understand the nature of selectivity in Ti-mediated reductive cross-coupling between homoallylic alcohols and imines, we investigated whether thermodynamic equilibration of the presumed organometallic intermediate plays a role in selectivity. No evidence could be found for olefin exchange in preformed azatitanacyclopentanes – an observation that is consistent with a model based on kinetically controlled selective carbometalation.

Reductive cross-coupling is emerging as a powerful strategy for bimolecular C–C bond formation.[1] This mode of reactivity has historically been limited to a relatively small substrate scope as a result of firmly established barriers associated with the control of reactivity and selectivity in the bimolecular C–C bond forming event.[2] In a program aimed at advancing a suite of methods for reductive cross-coupling that overcome these limitations, we recently described highly regio- and stereoselective coupling reactions of substituted homoallylic alcohols with aromatic imines (Figure 1).[3] This process, proceeding with stoichiometric use of an inexpensive and non-toxic metallic species (Ti(O*i*-Pr)₄), was accomplished by: 1) initial conversion of an aromatic imine to an azatitanacyclopropane, 2) introduction of a homoallylic alkoxide, and 3) protonation of the presumed bicyclic azametallacyclopentane intermediate. A mechanistic proposal to account for the enhanced reactivity and high selectivity observed was put forth based on: 1) rapid and reversible ligand exchange at titanium, and 2) site- and stereoselective intramolecular carbometalation under kinetic control.

During the course of these studies, we observed a stereoconvergence in reductive cross-coupling between disubstituted alkenes and aromatic imines. As illustrated in Figure 2, coupling of the homoallylic alcohol **7** or **8** with a simple aromatic imine provided the anti-1,5-amino alcohol **11** in 68 and 73% yield with very high levels of stereoselection (dr ≥ 95:5).[3] This observation was consistent with a mechanistic proposal whereby each alkene underwent selective carbometalation by way of distinct geometries (**I** and **II**). While the number of ligands on Ti in the transition state for these coupling reactions remains unclear, we expected that the development of a cis-fused bicyclo-[3.3.0] system would be favoured.[4] Further, minimization of eclipsing 1,2-interactions about the developing C–C bond was thought to be important for the control of stereochemistry *en route* to intermediates **9** and **10**. Subsequent protonation would then furnish the 1,5-amino alcohol **11**. Overall, the high anti-selectivity and stereoconvergence was consistent with this mechanistic proposal based on kinetic control.

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Previous reports in other laboratories have demonstrated that a variety of metallacyclopentane intermediates can readily undergo fragmentation with loss of an alkene ligand (Figure 3).[5,6] These observations led us to speculate whether the selectivity of our alkene–imine coupling was a result of thermodynamic, rather than kinetic, control.

Our studies aimed at addressing this question began with an analysis of the basic reaction process – we accepted that: 1) Ligand exchange at Ti was readily reversible and fast with respect to C–C bond formation,[7] and 2) azatitanacyclopentane formation followed from syn-carbometalation across the alkene. As depicted in Figure 4, if C–C bond-formation is readily reversible under the reaction conditions ($4 \rightleftharpoons 5$), then rapid and reversible ligand exchange at Ti should allow for alkene exchange ($4 \rightleftharpoons 15$). Subsequent carbometalation and protonation would then deliver 1,5-amino alcohol **17** from the preformed azametallacyclopentane **5**.

To determine whether such an alkene exchange could occur under the reaction conditions employed in our reductive cross-coupling, we explored the general reaction scheme depicted in Figure 5A. Here, metallacyclopentane intermediates with similar steric and electronic properties were sought to avoid biasing any potential equilibria. With this goal in mind, homoallylic alcohol **18** was coupled to imine **20** alongside the deuterated analogs **19** and **21**.[8,9] After reductive coupling was judged complete, the reaction mixtures were combined and stirred for an additional six hours at 0 °C to allow for equilibration. Subsequent hydrolysis of the presumed organometallic intermediates (H_2O) provided two of the four possible products (Figure 5B and 5C-I). Lack of evidence for D_5 (M +H = 275.2) or D_2 (M +H = 272.2)-containing products is consistent with the proposition that the equilibrium discussed in Figure 4 does not play a role in product distribution.

To confirm that the experimental procedure was sufficient for the conclusion reached, we needed to validate that quenching of the organometallic intermediates did not occurr during the mixing process. As such, a related experiment was performed where the organometallic intermediates were quenched with D_2O. In this experiment, only D_1 and D_8-containing products were identified (no evidence was found for the D_6 or D_3-containing cross-over products; Figure 5B and 5C-II).

In conclusion, we provide evidence that alkene exchange in titanium alkoxide-mediated reductive cross-coupling of imines with homoallylic alcohols does not occur under the reaction conditions described. Because rapid and reversible ligand exchange at Ti would allow for alkene exchange from mixed titanate esters (i.e. **4** and **15**), we conclude that carbometalation under these reaction conditions occurs in an irreversible manner. While more substituted alkenes may behave differently in this coupling process, the current study describes conclusive evidence in support of kinetic selectivity for the reductive cross-coupling of simple homoallylic alcohols with aromatic imines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Notes and references

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6. For related examples of C–C bond cleavage in metallacyclopentanes, see: a) McDermott JX, Wilson ME, Whitesides GM. J Am Chem Soc. 1976; 98:6529. b) Grubbs RH, Miyashita A. J Am Chem Soc. 1978; 100:1300. c) Dorf U, Engel K, Erker G. Angew Chem Int Ed Engl. 1982; 21:914. d) Cohen SA, Auburn PR, Bercaw JE. J Am Chem Soc. 1983; 105:1136. e) Cohen SA, Bercaw JE. Organometallics. 1985; 4:1006. f) Erker G, Czisch P, Kruger C, Wallis JM. Organometallics. 1985; 4:2059. g) Erker G, Dorf U, Rheingold AL. Organometallics. 1988; 7:138. h) Takahashi T, Tamura M, Saburi M, Uchida Y, Negishi E. J Chem Soc Chem Commun. 1989:852. i) Takahashi T, Fujimori T, Seki T, Saburi M, Uchida Y, Rousset CJ, Negishi E. J Chem Soc, Chem Commun. 1990:182. j) Ito H, Taguchi T, Hanzawa Y. Tetrahedron Lett. 1992; 33:4469. k) Taber DF, Louey JP, Lim JA. Tetrahedron Lett. 1993; 34:2243. l) Taber DF, Louey JP, Wang Y, Nugent WA, Dixon DA, Harlow RL. J Am Chem Soc. 1994; 116:9457. m) Harris MCJ, Whitby RJ, Blagg J. Tetrahedron Lett. 1995; 36:4287.

7. For a discussion of ligand exchange with titanium alkoxides, see: Woodard SS, Finn MG, Sharpless KB. J Am Chem Soc. 1991; 113:106.

8. In each case, 1.5 eq of homoallylic alcohol were used to ensure that, along with free isopropoxide (generated during the formation of the Ti-imine complex), the bicyclic metallacyclopentane intermediates have the potential to undergo ligand exchange with excess alkoxide.

9. For the preparation of **19**, see: a) Negishi E, Boardman LD, Sawada H, Bagheri V, Stoll AT, Tour JM, Rand CL. J Am Chem Soc. 1988; 110:5383.For the preparation of **20**, see: b) Simion A, Simion C, Kanda T, Nagashima S, Mitoma Y, Yamda T, Mimura K, Tashiro MJ. Chem Soc, Perkin Trans. 2001; 1:2071.
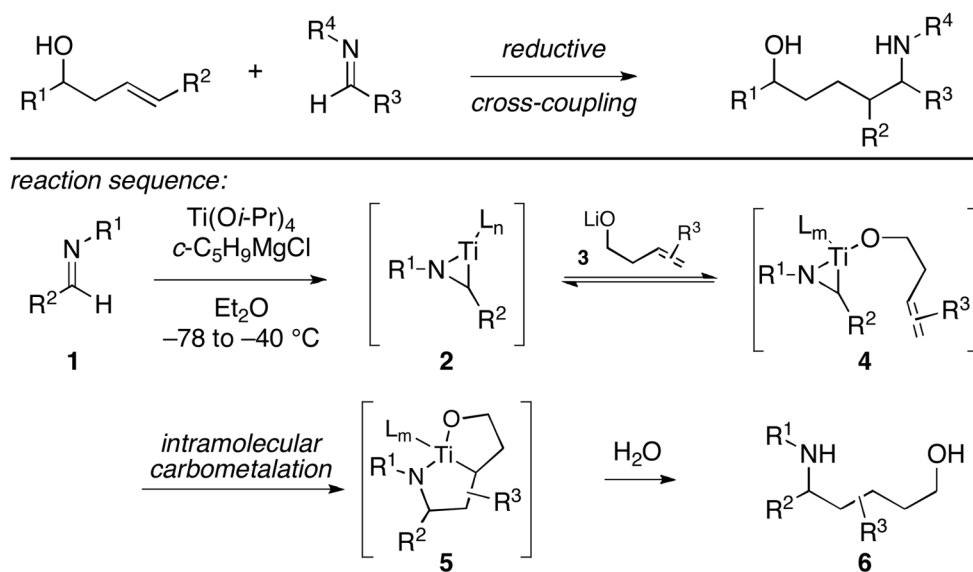
Figure 1.
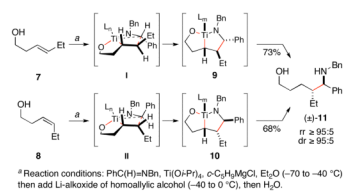Reductive cross-coupling of homoallylic alcohols with imines.

Figure 2.
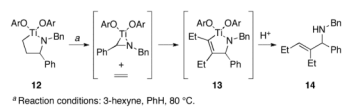Stereoconvergence in alkene–imine coupling.

Figure 3.
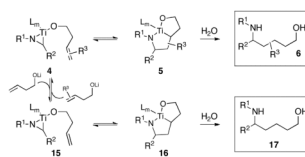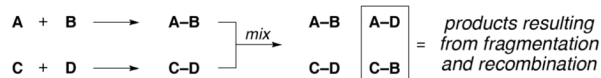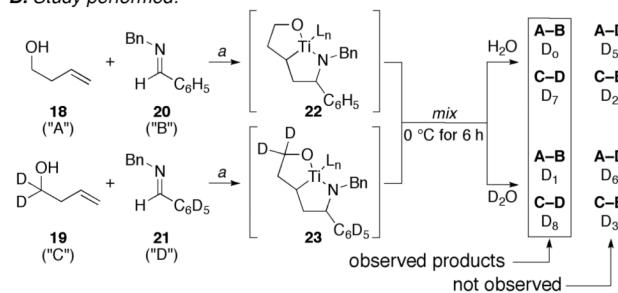C–C bond cleavage from a preformed azatitanacyclopentane.5

Figure 4.
Potential equilibria for alkene exchange.

A. *General reaction scheme:*

B. *Study performed:*

[a] Reaction conditions: Imine (1 equiv), $Ti(Oi\text{-}Pr)_4$, $c\text{-}C_5H_9MgCl$, Et_2O (−78 to −40 °C), then add Li-alkoxide of homoallylic alcohol (1.5 equiv) (−40 to 0 °C).

C. *LRMS of crude reaction mixture:*

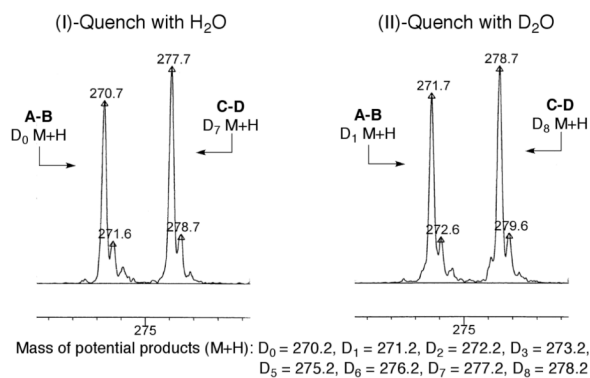Mass of potential products (M+H): $D_0 = 270.2$, $D_1 = 271.2$, $D_2 = 272.2$, $D_3 = 273.2$, $D_5 = 275.2$, $D_6 = 276.2$, $D_7 = 277.2$, $D_8 = 278.2$

Figure 5.
Cross-over experiments.