Asymmetric Catalysis

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Catalytic Enantioselective Alkynylation of Trifluoromethyl Ketones: Pronounced Metal Fluoride Effects and Implications of Zinc-to-Titanium Transmetallation**

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Propargylic alcohols are valuable intermediates in organic synthesis and pharmaceutical science.[1] Metal-catalyzed direct asymmetric addition of alkyne nucleophiles to aldehydes and prochiral ketones represents the most convergent and efficient approach to the synthesis of optically active propargylic alcohols.[2] The asymmetric titanium-catalyzed zinc alkynylide addition to carbonyl substrates has been extensively studied in the past decade, and numerous chiral ligands have been developed to give the desired propargylic alcohols in excellent enantioselectivity.[3] In spite of the importance of this practical transformation, some challenging problems remain unsolved. These problems include the stereochemical control for reactions involving challenging substrates as well as the mechanism of the putative zinc-to-titanium transmetallation, a key process in this type of asymmetric addition that has been reasonably implicated but remains largely unproven.

Trifluoromethyl ketones are a class of particularly challenging substrates for this asymmetric transformation because of the presence of the strongly electron-withdrawing fluorine atoms. The activating trifluoromethyl group renders the ketone functionality highly reactive and has a detrimental effect on the control of facial selectivity.[4] Although the asymmetric additions of alkyne nucleophiles to trifluoromethyl ketones have been well studied using stoichiometric chiral-auxiliary-based methods to control the absolute configuration,[5] to the best of our knowledge, there are no effective methods for catalyzing the asymmetric addition of alkynes to trifluoromethyl ketones.[6,7] We report herein a catalytic enantioselective addition of zinc alkynylides to various trifluoromethyl ketones with selectivities that surpass 94% *ee*. We demonstrate that with the application of pseudoenantiomeric cinchona alkaloids as chiral ligands, the synthesis of both enantiomers of the trifluoromethylated products is possible. Additionally, we provide the first experimental and computational evidence that the alkynyl group is bound to the titanium catalyst through transmetallation, and the organotitanium complex is responsible for the addition to trifluoromethyl ketones.

In an initial investigation, we conducted the reaction of the alkynylzinc, which was generated in situ from alkyne **4a** (see Table 1 for structure) and Et_2Zn, with 2,2,2-trifluoroacetophenone **3a** by employing (*S*)-3,3′-disubstituted binol (binol = 1,1'-bi-2-naphthol) ligands and (*S*,*S*)-taddol (taddol = tetraaryl-1,3-dioxolane-4,5-dimethanol) ligands to afford the desired adduct **5a** in quantitative yields and poor enantioselectivities (< 20% *ee*). Next, a large number of chiral amino alcohol ligands, which included DAIB [(2*S*)-(−)-3-*exo*-(dimethylamino)isoborneol], salen (*N*,*N*'-bis(salicylidene)ethylenediamine), cinchona alkaloids, ephedrine, prolinol, and some of their derivatives, were screened for the $Ti(OR)_4$-catalyzed alkynylation of **3a**. It was found that the pseudoenantiomeric cinchona alkaloids **1b** and **2b** were the most promising ligands for the test reaction (Table 1, entries 1–6), whereas all the other chiral ligands tested resulted in poor yields or enantioselectivities (not listed in Table 1). Interestingly, the introduction of CaH_2 as a base was found to significantly increase the conversion and selectivity for the reaction catalyzed by quinine **1b** (entry 7). The replacement of diethylzinc with dimethylzinc further improved the result (81% yield and 80% *ee*; entry 8). By using the same reaction conditions as used in entry 8, chiral alkaloid ligands such as DHQD (**1c**), CPN (**1d**), and BnOPN (**1e**) showed lower conversion and diminished enantioselectivity (entries 9–11). The superior level of asymmetric induction and reaction efficiency exhibited by the $Ti(OiPr)_4$/cinchona alkaloid catalyst upon addition of CaH_2 prompted us to examine the effect of various other additives. In view of the similarity in the nature of the hydride and the fluoride anions,[8] we expected that the use of a fluoride salt could have a comparable effect on the selectivity. Therefore a number of metal fluorides were subsequently examined (entries 12–17). Pleasingly, the use of BaF_2 led to a 90% yield of the isolated adduct (*R*)-**5a** with 87% *ee*. This beneficial effect was found to be sensitive to the metal center because metal ions of different sizes and Lewis acidity relative to barium imparted a deleterious impact on the enantioselectivity. Other barium salts including $BaCl_2$ and $BaBr_2$ were found to exhibit low levels of conversion and selectivity (entries 18 and 19). The pronounced rate and selectivity enhancement obtained when using BaF_2 probably stems from the good π-donating properties of fluoride, which could coordinate to titanium(IV) to

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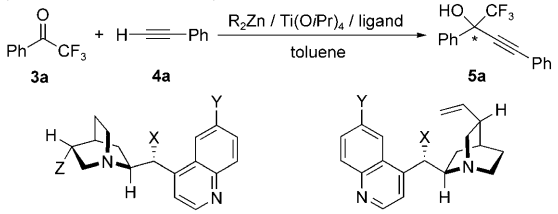
Table 1: The reaction conditions for the catalytic enantioselective alkynylation of trifluoromethyl ketones.[a]



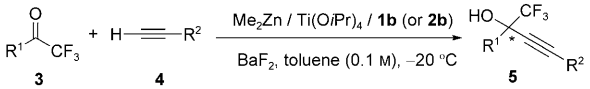
1a: X = OH, Y = H, Z = C_2H_3 (CD)
1b: X = OH, Y = OMe, Z = C_2H_3 (QN)
1c: X = OH, Y = OMe, Z = C_2H_5 (DHQD)
1d: X = OH, Y = OH, Z = C_2H_3 (CPN)
1e: X = OBn, Y = OH, Z = C_2H_3 (BnOPN)

2a: X = OH, Y = H (CN)
2b: X = OH, Y = OMe (QD)

Entry	Ligand	Additive (equiv)	*T* [°C]	Yield [%][b]	*ee* [%][c]
1[d]	**1a**	–	25	41	27 (*R*)
2[d]	**1b**	–	25	70	49 (*R*)
3[d]	**2a**	–	25	30	39 (*S*)
4[d]	**2b**	–	25	72	53 (*S*)
5[d]	**1b**	–	0	70	50 (*R*)
6[d]	**1b**	–	−20	68	53 (*R*)
7[d]	**1b**	CaH_2 (0.6)	−20	76	78 (*R*)
8[e]	**1b**	CaH_2 (0.6)	−20	81	80 (*R*)
9[e]	**1c**	CaH_2 (0.6)	−20	75	73 (*R*)
10[e]	**1d**	CaH_2 (0.6)	−20	69	68 (*R*)
11[e]	**1e**	CaH_2 (0.6)	−20	41	40 (*R*)
12[e]	**1b**	CsF (0.6)	−20	95	3
13[e]	**1b**	TiF_4 (0.6)	−20	73	12 (*R*)
14[e]	**1b**	CaF_2 (0.6)	−20	85	86 (*R*)
15[e]	**1b**	MgF_2 (0.6)	−20	90	84 (*R*)
16[e]	**1b**	SrF_2 (0.6)	−20	57	53 (*R*)
17[e]	**1b**	BaF_2 (0.6)	−20	90	87 (*R*)
18[e]	**1b**	$BaCl_2$ (0.6)	−20	29	39 (*R*)
19[e]	**1b**	$BaBr_2$ (0.6)	−20	30	23 (*R*)
20[e]	**1b**	BaF_2 (0.6)	−40	70	84 (*R*)
21[e]	**1b**	BaF_2 (0.3)	−20	96	84 (*R*)
22[e]	**1b** (QN)	BaF_2 (0.2)	−20	89	91 (*R*)
23[e]	**2b** (QD)	BaF_2 (0.2)	−20	86	84 (*S*)

[a] General reaction conditions: **3a**/**4a**/Et_2Zn/$Ti(OiPr)_4$/ligand = 1.0:2.5:3.0:2.0:0.2 in toluene (0.1 M), for 2 days. [b] Yield of isolated product. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase. The absolute configuration is based on the comparison of the optical rotation with the literature.[6] [d] Et_2Zn was used. [e] Me_2Zn was used.

Table 2: Catalytic enantioselective alkynylation of trifluoromethyl ketones.[a]



Entry	Ligand	R^1, R^2 (Product **5**)	Yield [%][b]	*ee* [%][c]
1	**1b**	Ph, Ph (**5a**)	89	91 (*R*)
2	**2b**	Ph, Ph (**5a′**)	86	84 (*S*)
3	**1b**	4-FC_6H_4, Ph (**5b**)	95	90 (*R*)
4	**2b**	4-FC_6H_4, Ph (**5b′**)	92	86 (*S*)
5	**1b**	4-ClC_6H_4, Ph (**5c**)	98	88 (*R*)
6	**2b**	4-ClC_6H_4, Ph (**5c′**)	98	84 (*S*)
7[d]	**1b**	4-BrC_6H_4, Ph (**5d**)	69	86 (*R*)
8[d]	**2b**	4-BrC_6H_4, Ph (**5d′**)	68	85 (*S*)
9[d]	**1b**	4-MeC_6H_4, Ph (**5e**)	82	85 (*R*)
10[d]	**2b**	4-MeC_6H_4, Ph (**5e′**)	82	85 (*S*)
11[d]	**1b**	3,5-$Me_2C_6H_4$, Ph (**5f**)	89	88 (*R*)
12[d]	**2b**	3,5-$Me_2C_6H_4$, Ph (**5f′**)	86	80 (*S*)
13[d]	**1b**	4-$MeOC_6H_4$, Ph (**5g**)	81	86 (*R*)
14[d]	**2b**	4-$MeOC_6H_4$, Ph (**5g′**)	81	82 (*S*)
15	**1b**	4-PhC_6H_4, Ph (**5h**)	93	83 (*R*)
16	**2b**	4-PhC_6H_4, Ph (**5h′**)	94	86 (*S*)
17[e]	**1b**	2-naphthyl, Ph (**5i**)	76	89 (*R*)
18[e]	**2b**	2-naphthyl, Ph (**5i′**)	80	83 (*S*)
19	**1b**	Ph, 4-FC_6H_4 (**5j**)	98	80 (*R*)
20	**2b**	Ph, 4-FC_6H_4 (**5j′**)	98	76 (*S*)
21	**1b**	4-MeC_6H_4, 4-FC_6H_4 (**5k**)	93	83 (*R*)
22	**2b**	4-MeC_6H_4, 4-FC_6H_4 (**5k′**)	95	84 (*S*)
23	**1b**	Ph, 4-MeC_6H_4 (**5l**)	98	84 (*R*)
24	**2b**	Ph, 4-MeC_6H_4 (**5l′**)	98	84 (*S*)
25	**1b**	4-ClC_6H_4, 4-MeC_6H_4 (**5m**)	98	85 (*R*)
26	**2b**	4-ClC_6H_4, 4-MeC_6H_4 (**5m′**)	98	80 (*S*)
27	**1b**	4-$MeOC_6H_4$,4-MeC_6H_4 (**5n**)	86	87 (*R*)
28	**2b**	4-$MeOC_6H_4$,4-MeC_6H_4 (**5n′**)	88	84 (*S*)
29	**1b**	Ph, cyclopropyl (**5o**)	96	65 (*R*)
30	**1b**	Ph, *n*-Hex (**5p**)	75	94 (*R*)
31	**1b**	*trans*-PhCH=CH, Ph (**5q**)	67	66 (*R*)
32[f]	**1b**	Ph, Ph (**5r**)	98	67 (*R*)
33[g]	**1b**	Ph, Ph (**5s**)	55	88 (*R*)

[a] General reaction conditions: **3**/**4**/Me_2Zn/$Ti(OiPr)_4$/**1b** or **2b**/BaF_2 = 1.0:2.5:3.0:2.0:0.2:0.2, in toluene (0.10 M) at −20 °C for 2 days. [b] Yield of the isolated products. [c] The *ee* values were determined by HPLC analysis. The absolute configuration of **5a** and **5a′** is based on the comparison of the optical rotation with the literature values.[6] The absolute configuration of other adducts were assigned on the basis of analogy with **5a** and **5a′**. [d] 3 days. [e] 5 days. [f] α,α-Difluoroacetophenone was used as the substrate. [g] Pentafluoroethyl phenyl ketone was used as substrate.

cause the deoligomerization of the catalyst structure, thus forming a more favorable catalytic precursor.[9] A decrease in the loading of BaF_2 led to the best result [(*R*)-**5a** in 89 % yield and 91 % *ee*; entry 22]. Under similar reaction conditions, the use of QD (**2b**) as the chiral ligand gave the *S*-configured adduct **5a′** with 84 % *ee* (entry 23). Additional solvent screening demonstrated that toluene was the optimal solvent under the reaction conditions used.

On the basis of these results, QN (**1b**) and QD (**2b**) were ultimately selected as the ligands and BaF_2 as the additive for the reaction of trifluoromethyl ketones **3** with terminal alkynes **4** in the presence of $Ti(OiPr)_4$ to give either enantiomer of **5**. Results in Table 2 indicate that both enantiomers of the desired adducts can be synthesized by using **1b** and **2b** to give (*R*)-**5** and (*S*)-**5**, respectively, with good to high yield and enantioselectivity. The reaction can tolerate a wide range of functional groups on ketones **3** and alkynes **4**, including electron-neutral, electron-withdrawing, and electron-donating groups (entries 1–28). For ketones **3** that have electron-donating groups and a bromide substituent on the aromatic ring, a somewhat prolonged reaction time was required to get satisfactory yields (entries 7–14, 17, and 18). It is noteworthy that aliphatic alkynes also gave the adducts in good to high yield and enantioselectivity (entries 29 and 30). Additionally, the reaction worked well with (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one to afford the 1,2-adduct in good yield and enantioselectivity (entry 31). To further define the scope of our methodology, the reactions of difluoromethyl- and perfluoroethyl ketones were also tested. The reaction of α,α-difluoroacetophenone proceeded in

quantitative yield and good enantioselectivity (entry 32). Perfluoroethyl phenyl ketone gave a moderate yield whilst maintaining a high *ee* value (entry 33). We also investigated the reaction with 2-fluoroacetophenone and acetophenone. These less reactive substrates were found to be unsuitable for this asymmetric transformation and only a racemic mixture of products were obtained in poor yields (< 15 %). Additionally, a sterically hindered ketone was found to give a good yield but a low *ee* value.[10]

To cast some light on the mechanism and to identify the role of the fluoride additive, electrospray ionization mass spectrometry (ESI-MS) methods were used to study this 1,2-addition reaction. An ESI-MS measurement of a mixture of $Ti(OiPr)_4$, QN (**1b**), phenylacetylene (**4a**), BaF_2, and Me_2Zn (2.0:0.2:2.5:0.2:3) in toluene displayed a base peak at *m*/*z* 765.4, pertaining to the existence of the zinc-to-titanium transmetallation intermediate [Ti(O*i*Pr)$_2$(phenyl ethynyl)-(quininyl)BaF_2] (**I**, Figure 1). When the amount of Me_2Zn in the mixture was increased to six equivalents, the ESI-MS experiment gave a new base peak at *m*/*z* 721.4, thus pointing to the bis(transmetallated) product [MeTi-(O*i*Pr)(phenylethynyl) (quininyl)BaF_2] (**II**, Figure 1).

To gain a better understanding of this reaction, DFT calculations using the B3LYP/6-31G(d) method[11] were performed with a view of delineating the details of the putative zinc-to-titanium transmetallation. The computed route of the model reaction between the simplified titanium(IV)/amino-alcohol complex **III** and methyl(phenylethynyl)zinc is shown in Figure 2.[12] Given the pronounced effect of BaF_2 in improving both the yield and the enantioselectivity of the reaction, and the ESI-MS results, which indicate the participation of BaF_2 in the formation of the transmetallation products **I** and **II** (Figure 1), the calculation was based on the heterobinuclear metal center IN1 as the platform for the subsequent transmetallation. The formation of IN1 was found to be strongly exothermic, both in gas phase and in solution

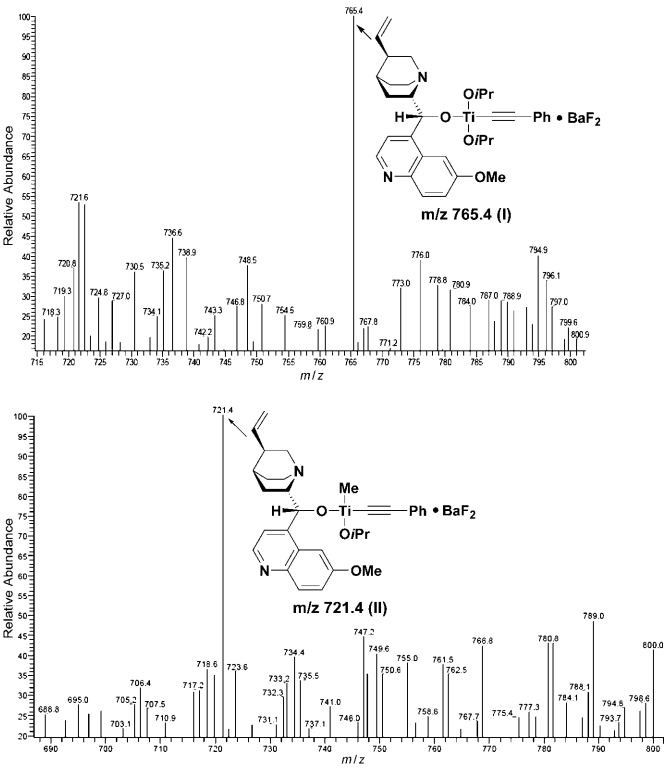


Figure 1. ESI-MS experiment of the intermediates (**I**) and (**II**).

(toluene). Complexation of methyl(phenylethynyl)zinc with the isopropoxy ligand on IN1 to give IN2 is also exothermic and helps bring the reaction to its energy minima. Formation of the first transmetallation intermediate IN3 from the ligand-bound organozinc IN2 proceeds through a concerted process featuring a zinc-to-titanium migration of the alkynyl group crossing an oxygen bridge (TS), with an energy barrier of 25.5 kcal mol^{-1} in solution. Although significant, this

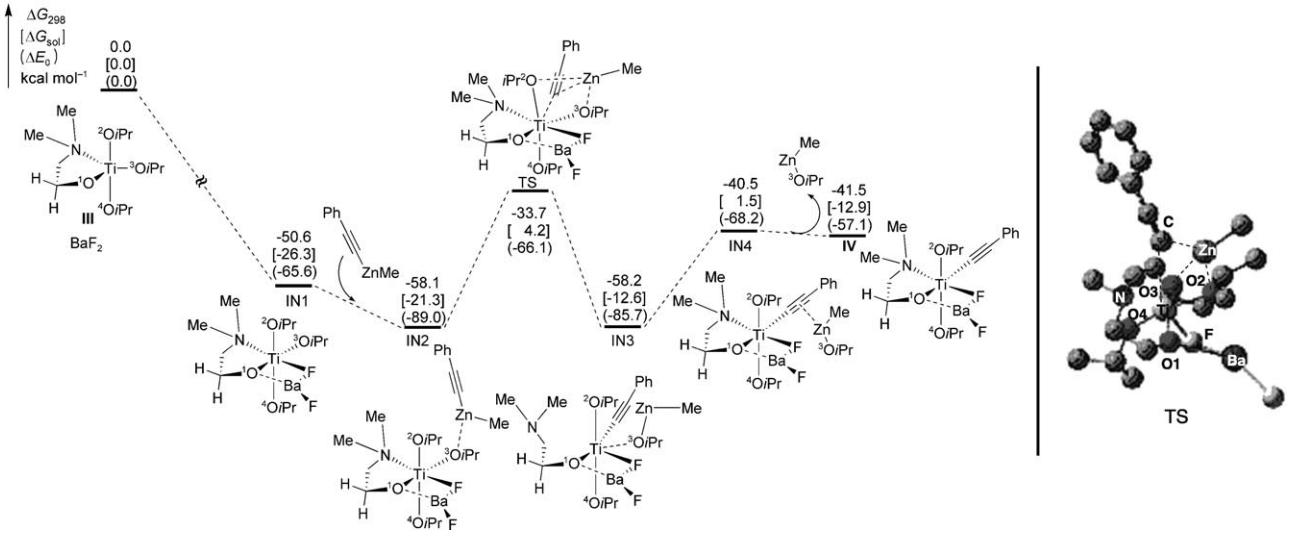
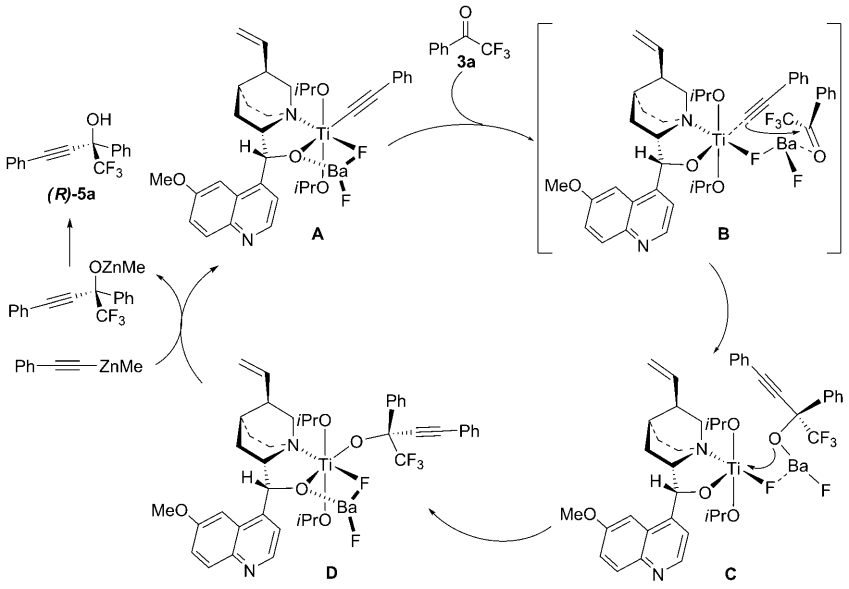


Figure 2. The DFT computed energy surfaces considered for zinc-to-titanium transmetallation. The values listed for each structure represent $\triangle G_{298}$, $\triangle G_{sol}$, and $\triangle E_0$, respectively, in kcalmol^{-1}. Calculated bond lengths [Å]: Ti–N 2.532, Ti–O(1) 1.992, Ti–O(2) 2.146, Ti–O(3) 1.940, Ti–F 1.920, Ti–C 2.785, Ba–O(1) 2.744, Ba–F 2.553, Zn–O(2) 2.270, Zn–O(3) 2.076.



Scheme 1. Proposed mechanism and transition-state models for the alkynylation of **3a** into **5a**.

energy requirement is more than compensated for by the energy released in the preceding steps (from **III** to IN2). Furthermore, formation of IN3 from IN2 is nearly thermodynamically neutral and its subsequent conversion into the final transmetallation product **IV** through the intermediacy of IN4 is only slightly endothermic. Therefore, the overall process for the formation of complex **IV** is exothermic and thermodynamically favorable.

The combination of the structure **I** observed by the ESI-MS experiments (Figure 1) and the DFT optimized structure **IV** (Figure 2) allows proposal of the hitherto putative transmetallation intermediate **A** for the reaction of phenylacetylene and 2,2,2-trifluoroacetophenone using **1b** as the chiral ligand (Scheme 1). The mechanistic pathway for the formation of (*R*)-**5a** includes the following steps: a) barium(II)-assisted addition of the chiral organotitanium species to the *Re* face of the trifluoromethyl ketone substrate via the cyclic transition-state **B** to give the barium(II) alkoxide intermediate **C**; b) barium-to-titanium shift of the alkoxy group to generate the titanium(IV) alkoxide intermediate **D**; and c) transmetallation of methyl(phenylethynyl)zinc with **D** to regenerate the organotitanium intermediate **A**.

In summary, we have successfully developed an efficient titanium(IV)-catalyzed enantioselective alkynylation of trifluoromethyl ketones by utilizing chiral cinchona alkaloids as ligands.[13] The major advantage of this process is that both enantiomers of trifluoromethylated propargylic tertiary alcohols can be accessed in good to high yields (up to 98%) and enantioselectivities (up to 94% *ee*) from cheap and commercially available chiral ligands. Most significant of all is the remarkable effect of the metal fluoride additive, which has proven to be essential for effective asymmetric induction. Moreover, we present the first piece of evidence for the mechanism of the zinc-to-titanium transmetallation in a titanium(IV)-catalyzed enantioselective alkynylation reaction. The use of fluoride additives in other transition-metal-catalyzed processes as well as additional mechanistic studies are underway in our laboratory.[14]

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[1] For selected reviews, see: a) *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**; b) N. Ljungdahl, N. Kann, *Angew. Chem.* **2009**, *121*, 652–654; *Angew. Chem. Int. Ed.* **2009**, *48*, 642–644; c) D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149–4158.

[2] For recent reviews, see: a) L. Pu, *Tetrahedron* **2003**, *59*, 9873–9886; b) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095–4105; c) D. J. Ramón, M. Yus, *Angew. Chem.* **2004**, *116*, 286–289; *Angew. Chem. Int. Ed.* **2004**, *43*, 284–287; d) J. M. Betancort, C. García, P. J. Walsh, *Synlett* **2004**, 749–760; e) G. Lu, Y.-M. Li, X.-S. Li, A. S. C. Chan, *Coord. Chem. Rev.* **2005**, *249*, 1736–1744; f) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963–983; g) L. Lin, R. Wang, *Curr. Org. Chem.* **2009**, *13*, 1565–1576.

[3] For recent examples of titanium complexes as catalysts in asymmetric alkynylation, see: a) G. Gao, R.-G. Xie, L. Pu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5417–5420; b) D. Moore, L. Pu, *Org. Lett.* **2002**, *4*, 1855–1857; c) G. Gao, D. Moore, R.-G. Xie, L. Pu, *Org. Lett.* **2002**, *4*, 4143–4146; d) G. Lu, X. Li, W. L. Chan, A. S. C. Chan, *Chem. Commun.* **2002**, 172–173; e) X.-S. Li, G. Lu, W. H. Kwok, A. S. C. Chan, *J. Am. Chem. Soc.* **2002**, *124*, 12366–12367; f) L. Lin, X. Jiang, W. Liu, L. Qiu, Z. Xu, J. Xu, A. S. C. Chan, R. Wang, *Org. Lett.* **2007**, *9*, 2329–2332.

[4] For recent reviews, see: a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**; b) Special Issue on "Fluorine in the Life Sciences", *ChemBioChem* **2004**, *5*, 557–726; c) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, UK, **2004**; d) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; e) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1–43; f) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305–321; g) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455–529.

[5] a) A. S. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 8937–8940; b) A. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, J. F. Remenar, D. B. Collum, *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038; c) L. Tan, C. Chen, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Angew. Chem.* **1999**, *111*, 724–727; *Angew. Chem. Int. Ed.* **1999**, *38*, 711–713; d) F. Xu, R. A. Reamer, R. Tillyer, J. M. Cummins, E. J. J. Grabowski, P. J. Reider, D. B. Collum, J. C. Huffman, *J. Am. Chem. Soc.* **2000**, *122*, 11212–11218; e) B. Jiang, Y. Feng, *Tetrahedron Lett.* **2002**, *43*, 2975–2977.

[6] We are aware of one catalytic but only moderately enantioselective alkynylation of trifluoromethyl ketones using copper complexes. In this case, a very limited range of substrates were tested and only moderate enantioselectivity was observed, see:

R. Motoki, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 2997 – 3000.

[7] For biocatalytic kinetic resolution of racemic substrates for the preparation of chiral trifluoromethylated propargylic tertiary alcohols, see: a) B. Heinze, R. Kourist, L. Fransson, K. Hult, U. T. Bornscheuer, *Protein Eng. Des. Sel.* **2007**, *20*, 125 – 131; b) S. Bartsch, R. Kourist, U. T. Bornscheuer, *Angew. Chem.* **2008**, *120*, 1531 – 1534; *Angew. Chem. Int. Ed.* **2008**, *47*, 1508 – 1511.

[8] Hydride and fluoride are classified as hard ligands in coordination chemistry. In addition, the Van der Waals radius of fluorine of 1.35 Å renders this element only slightly larger (12.5 %) than hydrogen (1.20 Å).

[9] For selected reviews, see: a) B. L. Pagenkopf, E. M. Carreira, *Chem. Eur. J.* **1999**, *5*, 3437 – 3442; b) K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26 – 49; *Angew. Chem. Int. Ed.* **2002**, *41*, 26 – 47; for selected examples, see: c) D. R. Gauthier, E. M. Carreira, *Angew. Chem.* **1996**, *108*, 2521 – 2523; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363 – 2365; d) X. Verdaguer, U. E. W. Lange, M. T. Reding, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 6784 – 6785; e) J. Krüger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837 – 838; f) R. Dorta, P. Egli, F. Zürcher, A. Togni, *J. Am. Chem. Soc.* **1997**, *119*, 10857 – 10858; g) B. L. Pagenkopf, E. M. Carreira, *Tetrahedron Lett.* **1998**, *39*, 9593 – 9596.

[10] The enantioselective alkynylation of 2′-chloro-2,2,2-trifluoroaceto-phenone with phenylacetylene; adduct 85 % yield, 40 % *ee.* (by using QN).

[11] The B3LYP calculations were carried out according to Ahlrichs's SVP all electron basis set model using pseudo-potential basis sets (LAN2MB) for Ba, Zn, Ti, and 6-31G(d) basis set for C, H, O, N, F. Computational details and references are given in the Supporting Information.

[12] For several examples of a titanium(IV)/complex that contains the alkoxides and one tertiary amine donor, see: a) K.-H. Wu, H.-M. Gau, *Organometallics* **2004**, *23*, 580 – 588; b) L. Lavanant, L. Toupet, C. W. Lehmann, J.-F. Carpentier, *Organometallics* **2005**, *24*, 5620 – 5633; c) S.-H. Hsieh, H.-M. Gau, *Chirality* **2006**, *18*, 569 – 1574; d) J. K. Day, R. E. Baghurst, R. R. Strevens, M. E. Light, M. B. Hursthouse, B. F. Stengel, I. A. Fallis, S. Aldridge, *New J. Chem.* **2007**, *31*, 135 – 143.

[13] During the revision of this manuscript, a palladium-catalyzed enantioselective alkynylation of trifluoropyruvate was described: K. Aikawa, Y. Hioki, K. Mikami, *Org. Lett.* **2010**, *12*, 5716 – 5719.

[14] The enantioselective alkynylation of benzaldehyde with the complex **I** under unoptimized reaction conditions gave the adduct in quantitative yield with 70 % *ee.* We thank one of the reviewers for suggesting that we examine the reactivity of complex **I** towards the aldehyde substrate.

