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Communication

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Organotitanium Nucleophiles in Asymmetric Cross-Coupling Reaction: Stereoconvergent Synthesis of Chiral α-CF_3 Thioethers.

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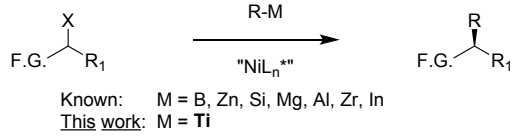
Supporting Information Placeholder

ABSTRACT: Asymmetric Ni-catalyzed cross-coupling reactions have become a very attractive tool for the stereoselective construction of valuable organic chiral materials. While various nucleophiles are used in such transformation, organotitanium (IV) has not been used before. Herein we demonstrate, for the first time, that organotitanium species can serve as efficient coupling partners in asymmetric cross-couplings, which have proven to be beneficial, compared to the commonly used organomagnesium and organozinc counterparts. This principle is exemplified by the first asymmetric catalytic synthesis of CF_3-substituted thioethers via a Ni-catalyzed stereoconvergent cross-coupling reaction. Thioether moieties and their derivatives are common motifs in many biologically-active compounds, and their enantioenriched fluorinated analogs should be of great interest in the search for novel drugs and agrichemicals.

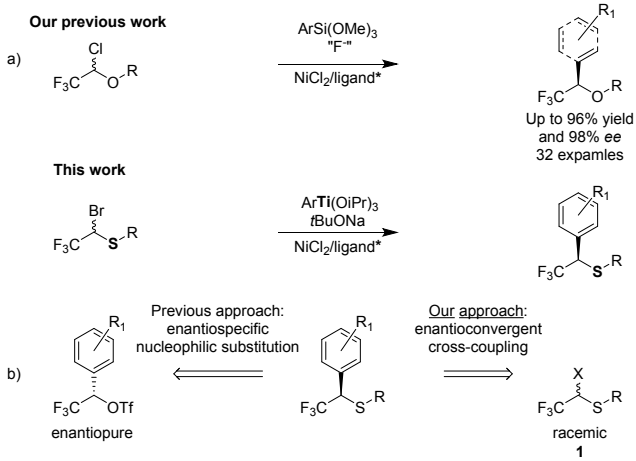
Cross-coupling reactions have become a major route for the construction of carbon-carbon bonds in organic molecules and materials. After a seminal work of Fu, the field of nickel-catalyzed enantioselective cross-couplings has emerged as a useful approach for the creation of stereo-defined chiral centers.[1] In a quest for the perfect method, different nucleophiles were employed under various conditions to incorporate the desired moieties into the target molecule containing diverse sensitive functional groups. Asymmetric cross-couplings are reported for nucleophiles based on organo-zinc,[2] boron,[3] magnesium,[4] silicon,[5] aluminum,[6] zirconium[7] and indium.[8] Between these species, organo-magnesium and zinc nucleophiles are largely employed in enantioselective cross-coupling reactions due to their fast transmetalation rates and ease of preparation. Nevertheless, due to their high basicity and nucleophilicity, organomagnesium reagents suffer from low functional group compatibility.[9] While organozinc reagents possess a relatively high functional group tolerance, in some cases the transmetalation from these nucleophiles could present a rate limiting step of the catalytic cycle.[10] This could be detrimental for some reactions involving alkyl-based electrophiles, since side processes such as β-H elimination, dehydrohalogenation, or metal-F elimination (in the species bearing fluoroalkyl substituents and involving an M-C-C-F oxidative addition intermediate) are possible. Therefore, attempts to utilize more selective, but less reactive, transmetalating agents may result in significant changes to the kinetics of the catalytic process,[11] providing an opportunity for undesired side reactions to occur. As such, the search for a compromise between functional group compatibility and the rate of transmetalation is essential for the success of the studied transformation.

We anticipated that the use of organotitanium reagents could be advantageous, since they possess a lower nucleophilicity and basicity compared to their magnesium counterparts, allowing a greater functional group tolerance; at the same time, these species have higher transmetalation rates than organozinc compounds. Knochel *et al.* demonstrated, that cross-couplings utilizing organotitanium reagents are significantly faster than those employing the corresponding organozinc counterparts.[12] Interestingly, while organotitanium (IV) compounds were extensively studied in nucleophilic addition to carbonyls,[13, 14] only very few examples of the employment of such reagents in *non*-asymmetric cross-coupling transformations are documented.[12, 15] To the best of our knowledge, the utilization of organotitanium nucleophiles in *asymmetric cross-coupling reactions* to create a stereogenic center is unprecedented.

Scheme 1. Nucleophiles in enantioconvergent cross-coupling reactions



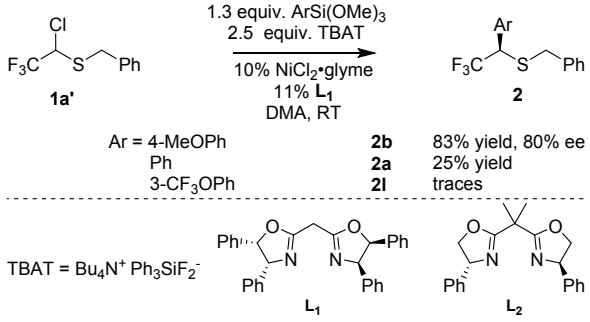
Scheme 2. Approaches towards α-CF_3-benzyl (thio)ethers



The site-selective introduction of fluorinated groups into drug molecules or drug candidates frequently leads to a substantial improvement in their biological properties.[16] Therefore, efficient methods for the regio- and stereoselective introduction of fluorinated moieties into organic functional compounds are in high demand in the search for new bioactive materials. Recently, we initiated an active program of the utilization of CF_3- and

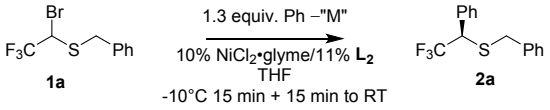
polyfluoroalkyl-substituted bisfunctionalized electrophiles in asymmetric cross-coupling transformations.[5b] Our approach allows for a rapid synthesis of chiral organic compounds bearing both a functional group and a fluoroalkyl substituent in the stereogenic center. To initially exemplify this principle, we have developed an approach towards enantioenriched α-trifluoromethyl alcohols and ethers via an enantioconvergent nickel-catalyzed Hiyama cross-coupling reaction, which provides the target compounds in excellent yields and enantioselectivities (Scheme 2a). Inspired by these results, we sought to expand our approach towards the corresponding sulfur analogues since thioether moieties and their derivatives (such as sulfoxides and sulfones) are common motifs in many biologically-active compounds.[17,18] The preparation of enantioenriched thioethers usually relies on the stereospecific nucleophilic substitution of stereodefined electrophiles with sulfur-based nucleophiles.[19] However, stereospecific nucleophilic substitution at the benzylic position bearing a trifluoromethyl group is challenging since the substrates are susceptible to racemization, depending on the reaction conditions and nature of the nucleophile (Scheme 2b).[20] Employing our approach, the desired products could be prepared via a stereoconvergent pathway starting from the racemic precursor **1**, which eliminates the need for the preparation of a stereodefined precursor. Herein, we report on a novel preparation of chiral (α-trifluoromethyl)benzyl thioethers in high yields and enantioselectivities via an asymmetric cross-coupling reaction utilizing aryltitanium nucleophiles. The approach can be extended to the preparation of enantioenriched perfluoroalkyl substituted thioethers. To the best of our knowledge, this is the first example of the utilization of organotitanium nucleophiles in asymmetric cross-coupling reactions.

Scheme 3. Hiyama cross-coupling reaction approach



Initially we attempted to prepare the desired thioether **2** by the Hiyama reaction, under conditions that we developed for the synthesis of the corresponding ethers.[5b] The model reaction of substrate **1a'** with 4-methoxyphenyl(trimethoxy)silane furnished the product **2b** in a promising yield of 83% and 80% ee (Scheme 3). However, the reaction with phenyl(trimethoxy)silane resulted in product **2a** in 25% yield, while the reaction with 3-trifluoromethoxyphenyl (trimethoxy)silane gave only traces of the cross-coupling product **2l**. Further analysis revealed that the target thioethers, especially those bearing electron-deficient aryls, are prone to the elimination of HF under basic Hiyama cross-coupling conditions followed, by further decomposition of the elimination product. This forced us to examine other nucleophiles for this reaction.

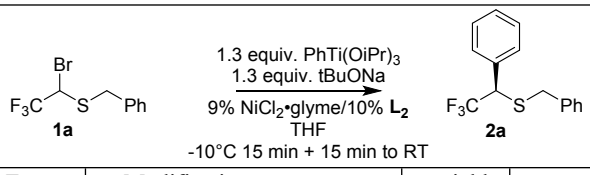
Scheme 4. Choice of organometallic nucleophiles



"M" =	Yield (conversion)	ee
ZnI•LiCl	72% (100%)	95%
MgBr	67% (70%)	92%
MgBr + $Ti(OiPr)_4$	88% (100%)	96%

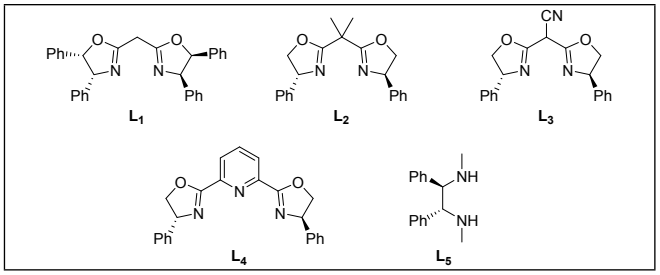
Promising preliminary results were obtained for organozinc compounds. Thus, after an initial examination of the reaction conditions, compound **2a** was obtained in a moderate yield and a high ee when the cross-coupling with PhZnBr was performed employing a catalytic system of $NiCl_2$ and ligand $\mathbf{L_2}$ (Scheme 4). However, the reaction was accompanied by a substantial production of homocoupled and other unidentified by-products. On the other hand, an aryl Grignard reagent, utilized under the same reaction conditions, led to a similar output, and the yield of the product **2a** was equivalent to the conversion (Scheme 4). However, the reaction did not go to completion even after a prolonged reaction time, presumably due to the deactivation of the catalytic system with PhMgBr. The selectivity of the Grignard reagent was improved by its prior mixing with $Ti(OiPr)_4$, which, in effect, was the formation of the organotitanium active species (Scheme 4).[12] This led us to examine independently prepared aryl titanium (IV) compounds in this transformation.[21] Notably, $PhTi(OiPr)_3$ gave significantly poorer results (55% yield and 61% ee, Table 1, entry 2) than the titanate species presumably formed in the mixture of PhMgBr and $Ti(OiPr)_4$. Gratifyingly, when $PhTi(OiPr)_3$ was reacted in the presence of t-BuONa to form a titanate complex, the thioether **2a** was obtained in a 95% yield and 97% ee (Table 1, entry 1). Notably, the high oxophilicity and formation of a stable -ate complex preclude the presence of the free alkoxide in the solution, which makes the reaction conditions compatible with base-sensitive thioethers of type **2**.

Table 1. Optimization of the reaction conditions



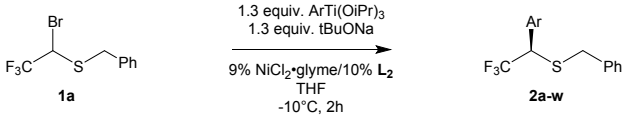
Entry	Modification	yield[a]	ee
1	None	93%	97%
2	Only $PhTi(OiPr)_3$	55%	61%
3	LiCl instead of tBuONa	81%	78%
4	EtONa instead of tBuONa	94%	94%
5	PhMgBr + $Ti(OiPr)_4$	87%	95%
6	PhMgBr + $Ti(OBu)_4$	92%	89%
7	rt instead of -10°C	66%	91%
8	No $NiCl_2$·glyme	-	-
9	No ligand	19%	-
10	Under air in closed vial	70%	95%
11	0.1 equiv. of H_2O	47%	89%
12	Ligand $\mathbf{L_1}$ instead of $\mathbf{L_2}$	26%	27%
13	Ligand $\mathbf{L_3}$ instead of $\mathbf{L_2}$	40%	51%
14	Ligand $\mathbf{L_4}$ instead of $\mathbf{L_2}$	6%	-
15	Ligand $\mathbf{L_5}$ instead of $\mathbf{L_2}$	17%	6%

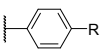
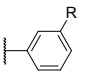
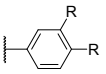
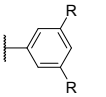
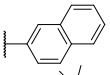
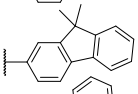
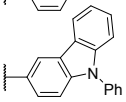
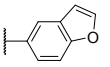
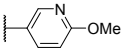
[a] – determined by ^{19}F NMR (with internal standard).



Any changes from the optimized conditions (entry 1) led to detrimental results. Thus, attempts to prepare the titanate complex by addition of LiCl to $PhTi(OiPr)_3$ furnished product **2a** in a 81% yield and 78% ee (entry 3). Sodium ethoxide provides similar results to those of tBuONa (94% yield and 94% ee; entry 4). The -ate complex can be prepared *in situ* from the corresponding Grignard reagent and titanium tetraisopropoxide or tetrabutoxide, furnishing slightly poorer yields and enantioselectivities (entries 5 and 6). The reaction performed at room temperature is significantly faster, providing substantially inferior results (entry 7). The presence of both the nickel salt and the ligand are necessary for the performance of the reaction (entries 8 and 9). While the reaction is moderately air sensitive, the addition of 0.1 equivalents of water significantly decreases the yield (entries 10 and 11).

Table 2. Scope of the aryl titanium partners



Entry		Ar	R	Yield [a]	ee
1	**2a**		H	87%	97%
2	**2b**		OMe	86% [b]	93%
3	**2c**		Ph	90%	98%
4	**2d**		$SiMe_3$	81%	96%
5	**2e**		Br	82%	98%
6	**2f**		CO_2Me	81% [c]	96%
7	**2g**		CN	72% [d]	94%
8	**2h**		$CH(OCH_2)_2$	86%	96%
9	**2i**		SMe	90%	99%
10	**2j**		OMe	83% (91%)[e]	97%(98%)[e]
11	**2k**		NMe_2	92%	97%
12	**2l**		OCF_3	83%	94%
13	**2m**		Cl, Cl	85% [f]	96%
14	**2n**		OCH_2O	81% [b]	92%
15	**2o**		OCF_2O	82% [f]	96%
16	**2p**		Me, Me	87%	97%
17	**2q**		CF_3, CF_3	82% [f]	97%
18	**2r**			93%	99%
19	**2s**			92%	99%
20	**2t**			86% [b]	96%
21	**2u**			76% [f]	95%
22	**2v**			48% [g]	56%
23	**2w**			47% [g]	71%

[a] – isolated yields (average of two runs); [b] – 1.5 equiv. of $ArTi(OiPr)_3$ and 1.5 equiv. of tBuONa; [c] – the ate complex was prepared in situ by a halogen-magnesium exchange with methyl 4-iodobenzoate followed by transmetalation to $Ti(OiPr)_4$; [d] – the ate complex was prepared in situ by a halogen-magnesium exchange with 4-bromobenzonitrile followed by transmetalation to $Ti(OiPr)_4$; [e] – reaction on 5 mmol scale(1.4 g) of starting **1a**; [f] – EtONa was used instead of tBuONa; [g] – without alkoxide.

Having established the optimal conditions, we subjected the substrate **1a** to the reaction with different aryl titanium nucleophiles (Table 2). To our delight, the scope of this transformation is significantly broad. The reaction proceeds smoothly with electron-rich and electron-poor aryl titanates, bearing various functional groups such as alkoxy, thioalkoxy, trimethylsilyl, tertiary anilines, halogens, trifluoromethoxy, protected aldehydes, nitriles and esters. While aryl Ti(IV) bearing meta and para- substituents on the aromatic ring performs excellently in this transformation, their counterparts with the *ortho*- substitution provides very low yields. Aryltitanium nucleophiles, bearing the electron-donating group in the *para*-position (see entries 2, 14, 20) show a diminished performance, giving rise to the formation of unidentified side products. The reaction can be improved by using slightly increased excess of the reagents (1.5 instead of 1.3 equivalents of both the aryl titanium and sodium *tert*-butoxide). In the case of highly electron poor aryltitaniums (entries 13, 15, 17), ate complex exhibits poor stability and hence an altered reactivity, what could be overcome by utilizing a sodium ethoxide suspension instead of soluble sodium *tert*-butoxide.[22] Aryl Ti(IV) bearing functional groups, such as ester[23] and nitrile, proved to be compatible with this cross-coupling reaction, however, under slightly midified conditions, since isolation of such $ArTi(OR)_3$ is problematic.[24] Heterocyclic aryl(triisopropoxy)titanium nucleophiles (entries 21-23) undergo a cross-coupling reaction, although the yields and enantioselectivities of the products are moderate.

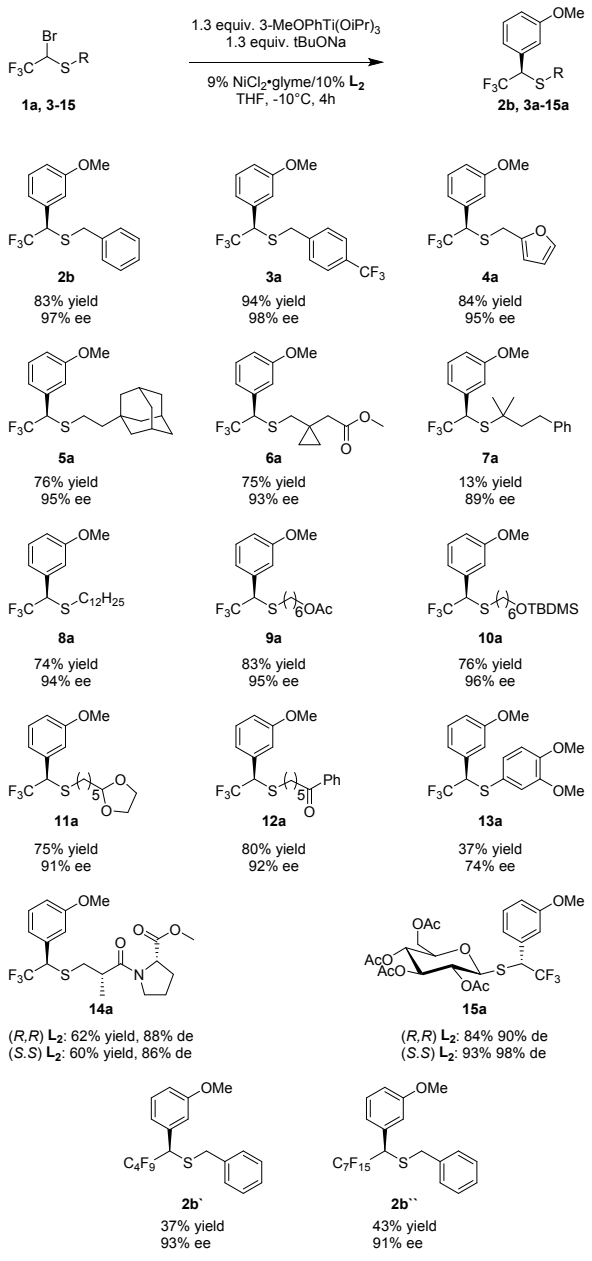
Notably, the reaction can be performed on a gram-scale with no significant difference in its effectiveness. Thus, when 5 mmol(1.43 g) of **1a** was cross-coupled with 3-MeOPhTi(OiPr)_3 under our standard conditions, the thioether **2b** was obtained in 91% yield and 98% ee (entry 10).

After exploring the scope of nucleophiles, we examined electrophiles bearing various thioether motifs (Scheme 5). To our delight, numerous functionalities are compatible with Ti (IV) nucleophiles in the cross-couplings under our reaction conditions. Esters, amides, silyl ethers, ketones and protected aldehydes having different distances from the reaction center, and even unfunctionalized substrates (see product **8a**) react efficiently to furnish products with excellent enantioselectivities and good yields. Benzylic thioethers exhibit faster reaction rates compared to alkyl substituted ones. While the reaction is complete within 2 hours for products **2a**, **3a**, **4b** and **15a**, approximately 5 hours are required to reach a full conversion for other products.

The reaction is not significantly sensitive to the steric bulk of the thioether substituent. Thus, the yields are high when the tertiary carbon center is located in either the β- or γ- positions (products **5a** and **6a**, correspondingly). However, in the case of a tertiary α-carbon, the desired product **7a** is obtained in only a 13% yield, although with an excellent ee. The main outcome of the reaction in the latter case is a homocoupled product. It should be noted that electrophiles derived from secondary thioethers perform efficiently in this cross-coupling reaction (**15a**). Aryl thioethers could also be prepared by this method, but in diminished yields and ee (product **13a**). Interestingly, it is possible to extend our approach to substrates bearing perfluoroalkyl chains instead of trifluoromethyl group in the

stereogenic center. The resulting compounds were obtained with excellent enantioselectivities, although the yields were only moderate (**2b`** and **2b``**). More complex compounds, for example derivatives of captopril (**14a**) and thiogluocose (**15a**) bearing multiple stereocenters in proximity to the thioether linkage could be efficiently utilized in this reaction, resulting in products with a high diastereomeric purity.

Scheme 5. Scope of thioethers



In conclusion, we have developed a novel asymmetric catalytic synthesis of CF_3-substituted thioethers by a Ni-catalyzed cross-coupling reaction, employing aryl titanium (IV) as a nucleophilic reagent. The method is compatible with various functional groups and the resulting products are usually obtained in high yields and enantioselectivities. To the best of our knowledge, this is the first example of the utilization of organotitaniums as nucleophiles in asymmetric cross-coupling reactions. Aryl titanium proved to be superior as a coupling partner in this particular transformation, compared to its closely related organomagnesium and organozinc counterparts. The added value of the organotitanium species in substrate-unrelated cross-coupling reactions, as well as the mechanistic studied of the presented method are under investigation in our labs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, NMR and HPLC spectra of new compounds (PDF).

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Notes

The authors declare no competing financial interests.

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18. For example, ones of the most selling drugs – Diltiazem, Montelukast, Tazobactam – possess a thioether function in the stereogenic center.

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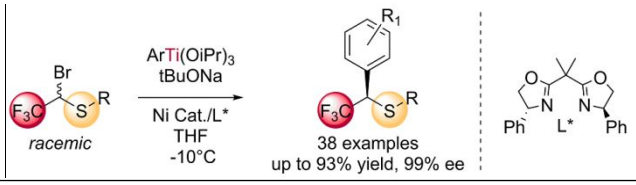
21. The aryltitaniums were prepared by reaction of chloro(triisopropoxy)titanium with corresponding arylmagnesium bromide in THF, followed by evaporation of the solvent and extraction with hexane. Concentration and cooling of the hexane extracts furnished precepitation of the aryl(triisopropoxy)titanium. For the detailed procedure see supporting information.

22. Persumably, sodium ethoxide is poorly soluble in tetrahydrofuran, but reacts selectively with an aryltitanium furnishing the corresponding ate complex in situ.

23. During the reaction was observed partial transesterification of methyl ester to isopropyl ester in extent of 5%

24. The whole three-step sequence was performed as one-pot procedure starting from the corresponding aryl halides: (1) halogen-magnesium exchange by the reaction of an aryl halide with i-PrMgCl·LiCl; (2) transmetallation of the resulting aryl Grignard reagent to $Ti(OiPr)_4$ to form aryl-titanate, and (3) Ni-catalyzed cross-coupling of the resulting aryl-titanate with the electrophile 1a. This indicates that the procedure is highly efficient (entries 6, 7) and tolerates the co-products of each step of the sequence, including secondary alkyl halides (formed in the first step).


Br
F3C
S
R
racemic
ArTi(OiPr)3
tBuONa
Ni Cat./L*
THF
-10°C
R1
F3C
S
R
38 examples
up to 93% yield, 99% ee
O
O
N
N
Ph
L*
Ph