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Synthesis of Chiral α-CF_3-Substituted Benzhydryls via Cross-Coupling Reaction of Aryltitanates

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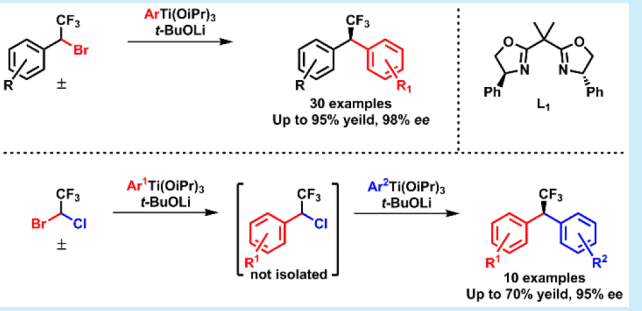
ABSTRACT: We describe a highly efficient approach toward α-CF_3-substituted benzhydryls thanks to the employment of organotitanium(IV) based nucleophiles. The use of commercially available anesthetic halothane as a cheap fluorinated building block in a sequential one-pot nickel-catalyzed enantioselective cross-coupling reaction of aryl titanates allowed for the synthesis of chiral α-CF_3-substituted benzhydryls in good yields and excellent enantioselectivities. Alternatively, α-CF_3-benzyl bromides could be employed under similar conditions to obtain the same family of compounds in higher yields and excellent selectivities. A benzhydryl moiety is a common motif in many biologically active compounds, and their enantioenriched fluorinated analogs should be of great interest in the search for novel drugs and agrochemicals.



Site-selective fluorination has become a widespread approach to alter features of a target compound.[1] Along with physical properties, fluorination significantly affects the reactivity and stability of a molecule and nearby functional groups.[2] These phenomena are of great utility for the agricultural and medicinal industries, as a tool for adjusting activity, bioavailability, and metabolic stability of a compound. Among other fluorinated moieties, the trifluoromethyl group is widely employed as a bioisoster for ethyl[3] and nitro[4] groups, as well as a substitute to a metabolically labile methyl group,[5] or to augment a lipophilicity of a target molecule. An increasingly growing demand for trifluoromethyl-containing motifs continuously leads to the exploration of new reaction pathways, including the use of alternative building CF_3-installing blocks. While the introduction of a trifluoromethyl group is not a trivial task, the need to create a CF_3-substituted stereogenic center in an enantioselective fashion significantly increases the complexity of this synthetic goal.[6]

Diarylmethanes is a widely encountered family of pharmacophores, and its utilization in an enantiopure form is especially important (Scheme 1a).[7] Therefore, development of asymmetric catalytic approaches to the synthesis of chiral 1,1-diarylmethanes gain much attention in the organic community.[8] Remarkably, synthesis of the compounds of type **1**, bearing the biomedically relevant CF_3 group at stereogenic center, in an enantioselective fashion is not a straightforward transformation[9] and only a few methods have been presented to date.[10] The synthesis of the motif **1** in an enantioenriched manner can be achieved via enantiospecific cross-coupling reaction of α-CF_3-benzyl tosylates[10a] or via recent elegant fluoroarylation of *gem*-difluoroalkenes.[10c] While our work on the synthesis of enantioenriched α-CF_3-substituted benzhydryls was in progress, Shen and co-workers reported an elegant approach to the synthesis of such compounds via an enantioconvergent nickel-catalyzed cross-coupling reaction of racemic α-CF_3-benzyl bromides with arylzincates, obtained *in situ* from corresponding boronates (Scheme 1b).[10b] This work represents the only reported approach for the enatioselective catalytic synthesis of compounds of type **1**. However, some substantial limitations should be noted: the method is limited to electron-poor electrophiles; a very high catalyst loading and a large excess of the transmetalating reagent should be used; additionally, utilization of butyllithium for the preparation of intermediate arylboronates limits the choice of functional groups installed in nucleophiles.

Recently we reported on the first utilization of titanium-based nucleophiles in an asymmetric cross-coupling reaction.[11] These reagents proved to be superior to their magnesium and zinc counterparts in the enantioselective synthesis of α-CF_3-benzyl thioethers, being a compromise between a high reactivity of organomagnesium species and a functional group tolerance of a corresponding organozinc reagent.[12] We wanted to expand the success of these reagents to other challenging transformations, such as a synthesis of α-CF_3-

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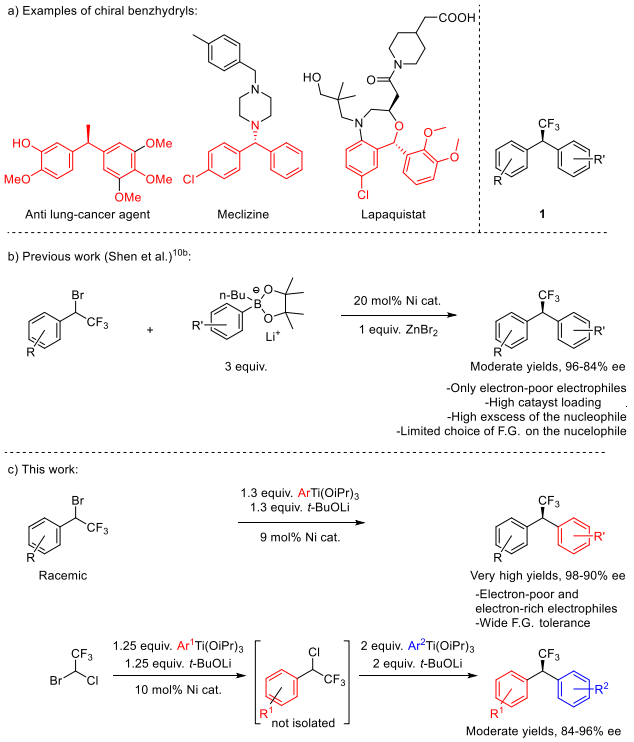
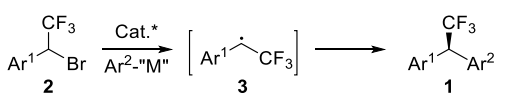
Scheme 1. Synthesis of Chiral α-CF_3-Substituted Benzhydryls



benzhydryles. In this letter we report on the utilization of aryltitanates in an enantioconvergent nickel-catalyzed cross-coupling reaction for a synthesis of chiral α-CF_3-substituted benzhydryls. To our delight, organotitanium nucleophiles proved to be very efficient reagents in this challenging transformation, allowing a number of aforementioned limitations and synthetic issues to be overcome. Notably, we describe here the use of halothane—an inexpensive commercially available anesthetic—as a fluorinated building block for the synthesis of α-CF_3-diarylmethanes via sequential enantioselective one-pot cross-coupling reactions of aryl titanates. Despite wide availability, the use of halothane as a CF_3-installing building block is not a common practice,[13] while its utilization in an enantioselective synthesis, to the best of our knowledge, is unprecedented.

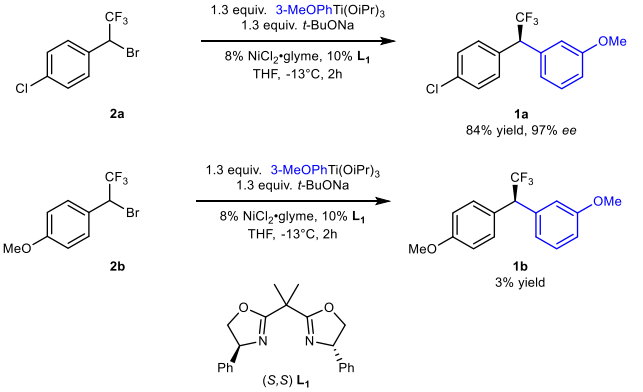
We have assumed that the proposed reaction follows the Ni(I)/Ni(III) radical mechanistic pathway elucidated for such type of cross-coupling processes by Fu and others.[14] The anticipated concept implies involvement of a substantially stabilized α-CF_3-benzyl radical **3** as a key reaction intermediate (Scheme 2).[15] While stabilization of the radical during cross-couplings usually is a beneficial factor for the reaction success,[16] an excessive stabilization can significantly impair the formation of the desired product. Presumably, this stability could lead to side reactions, including substantial homocoupling (*vide infra*), instead of coordination to the Ni center with the concomitant product-forming reductive elimination. Moreover, substituents on the aromatic ring directly influence the stability and reactivity of the radical **3** imposing difficulties on the generality of the desired approach.[17] Therefore, it imposes a considerable problem on the utilization of stabilized radicals of type **3**.

Scheme 2. Proposed Approach to the α-CF_3-Substituted Benzhydryls



We started investigation of the reaction from the choice of a model starting material. Reacting α-CF_3-4-chlorophenylbenzyl bromide **2a** with 3-MeOPhTi(OiPr)$_3$ and *t*-BuONa in the presence of a nickel precatalyst and bisoxazoline ligand **L1**, we were pleased to find that the desired compound can be obtained in an 85% yield and 97% *ee* (Scheme 3). However,

Scheme 3. Choice of a Model Electrophile



the use of 4-methoxy substituted electrophile **2b** provided the corresponding benzhydryl **1b** in 3% yield only. As a consequence of the relatively high stability of the radical, which derived from **2b**, the homocoupling of this electrophile was the main product of the reaction. Thus, **2b** was chosen as a model substrate for the further optimization of the reaction conditions.

After an extensive search we found that a LiCl additive has a prolific effect on the reaction outcome, increasing the yield up to 41% (Table 1, entry 2). Along with a yield, the use of the additive significantly increased the time required to reach a full conversion. The reaction conditions could be simplified by using lithium *tert*-butoxide instead of the *t*-BuONa/LiCl system without a compromise on the reaction outcome (entry 3).[18] Diglyme could be employed as a solvent instead of THF with a subtle improvement in the yield, although a slight decrease in enantioselectivity was observed (entry 4). Interestingly, the reaction performance can be improved by using aryltitanium(tris-*tert*-butoxide) as a nucleophile and 2 equiv of LiCl in the absence of the alkoxide base to 61%, although accompanied by high reaction time (entry 5). Notably, the highest reactivity for arylmagnesium and arylzinc reagents was also observed for the catalyst based on the ligand **L1**. However, these organometallic nucleophiles were inferior to the aryltitanate variant in the reaction with **2b** (entries 6 and 7).[19] The presence of the nickel precatalyst and ligand **L1** are both essential for the process (entries 8 and 9). Both air and moisture have a deleterious effect on the process (entries 10 and 11). The reaction can be performed at 0 °C, although the yield of **1b** is decreased (entry 12). Lowering the catalyst loading to 7% also diminishes the yield of **1b** (entry 13).[20]

Notably, our approach significantly improves the efficiency of the reaction of problematic electrophiles of type **2b** (bearing electron-donating substrates) compared to the previously reported approach (61% yield, 97% *ee* vs 25% yield, 80% *ee*).[10b]

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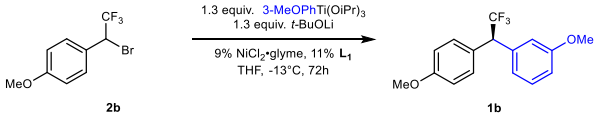
Table 1. Optimization of the Reaction Conditions[a,b]



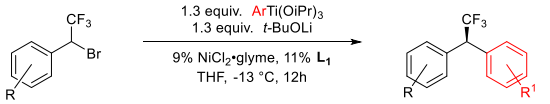
Entry	Variation	Yield of **1b** (%)	*ee* (%)
1[c]	*t*-BuONa instead of *t*-BuOLi	3	n.d.
2	*t*-BuONa, 2 equiv of LiCl as additives	41	96
3	none	43	97
4	Diglyme instead of THF	45	92
5[d]	$ArTi(OtBu)_3$ and 2 equiv of LiCl instead of $ArTi(OiPr)_3$ and *t*-BuOLi	61	97
6	ArMgCl instead of $ArTi(OiPr)_3$/*t*-BuOLi	9	n.d.
7	ArZnI instead of $ArTi(OiPr)_3$/*t*-BuOLi	8	n.d
8	No $NiCl_2$·glyme	traces	–
9	No L_1	4	–
10	Under air in a closed vial	traces	–
11	0.1 equiv of H_2O	16	95
12	0 °C instead of −13 °C	20	94
13	7% instead of 9% catalyst	26	96

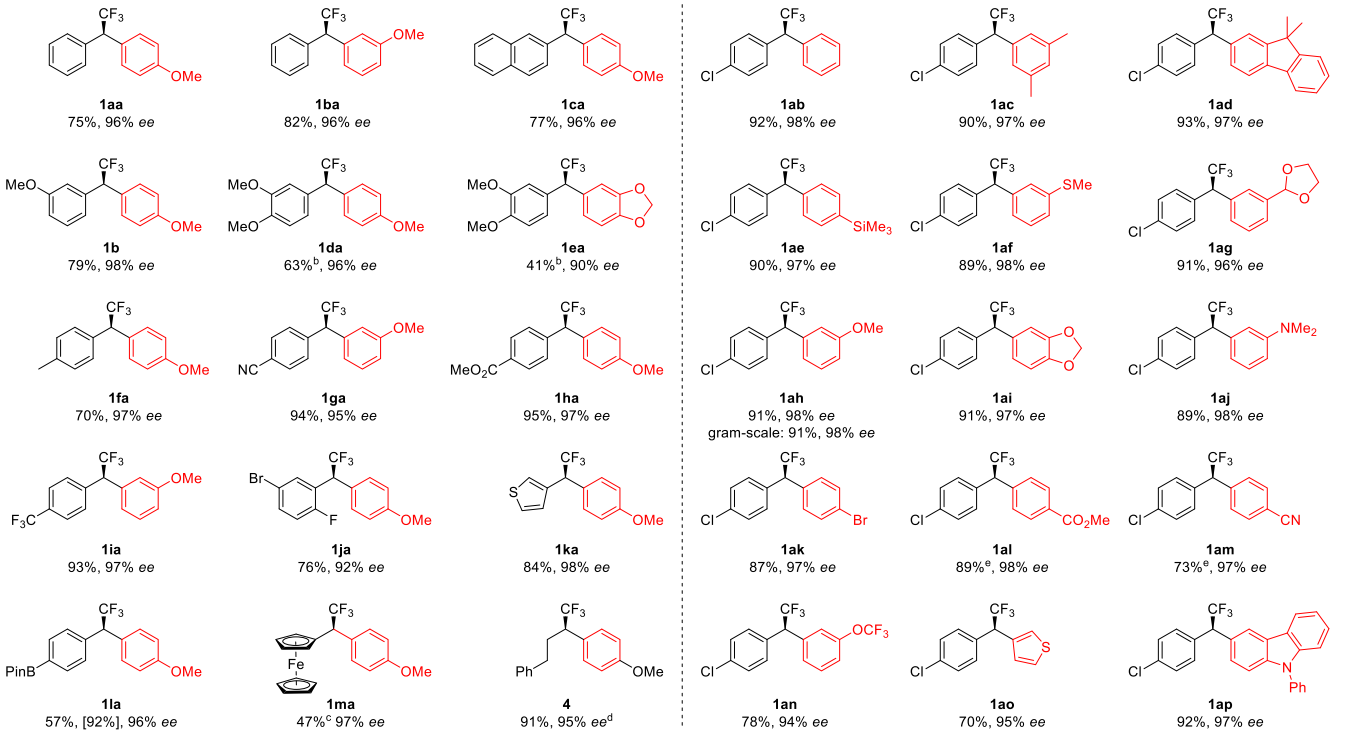
[a]Reactions performed on 0.0625 mmol scale. [b]Determined by ^{19}F NMR vs internal standard. [c]2 h reaction time. [d]120 h reaction time; n.d. – yield was not determined for reactions with a yield <10%.

Having a set of optimal conditions, we proceeded to the investigation of the reaction scope. $ArTi(OtBu)_3$/LiCl and $ArTi(OiPr)_3$/*t*-BuOLi systems performed similarly for most of the studied substrates, although the reaction time of the former system was significantly longer. Therefore, we employed the $ArTi(OiPr)_3$/*t*-BuOLi system, which allows completion of the reaction for most of the targeted substrates within 12 h. A variety of structurally and electronically diverse 1,1-diaryl-2,2,2-trifluoroethanes can be obtained in excellent yields and enantioselectivities (Scheme 4). Electrophiles bearing electron-withdrawing groups generally provide corresponding products in >90% yields. Gratifyingly, for electron-rich analogs—the problematic substrates in a previous approach—good yields were obtained with Ti(IV) nucleophiles. Even for very electron-rich electrophiles, bearing multiple alkoxy substituents (**1da**, **1ea**), practical yields were achieved. Substituents elsewhere on the aryl ring but in an *ortho*-position do not interfere with the reaction. Among *ortho*-substituted variants only starting materials, bearing a small substituent such as a fluorine atom, provide the desired product in a synthetically useful yield (**1ja**). Functional groups, such as esters, nitriles, halogens, and boropinacols are well tolerated. 3-Thienyl (**1ka**) or ferrocene-derived (**1ma**) electrophiles also can be efficiently employed in the developed process.[21]

The aryltitanium coupling partner can also be varied to a great extent. Aromatic motifs bearing both electron-withdrawing and electron-donating substituents can be introduced

Scheme 4. Scope of the Cross-Coupling Reaction of α-CF_3-Benzyl Bromides with Aryltitanates[a]





[a]Reactions were performed on a 0.5 mmol scale in duplicate. Isolated yields. NMR yields (if applicable) are given in square brackets. [b]Diglyme instead of THF. [c]−25 °C instead of −13 °C. [d]1,1,1-Trifluoro-2-bromo-4-phenylbutane as a starting material. [e]The aryl titanate was prepared *in situ*, starting from the corresponding aryl bromide or iodide; see SI for details.

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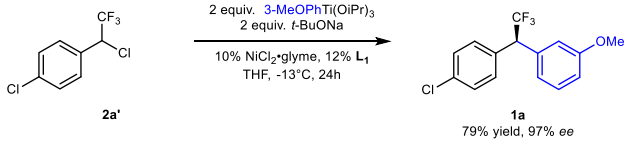
in high yields. Electron-rich aryl titanates provided products in slightly higher yields than the corresponding electron-poor counterparts. In the latter case yields were diminished in favor of the formation of the homocoupled product. The substitution pattern of the nucleophile favors *meta*- and *para*-substituents, while low conversion and a poor mass balance were observed for the *ortho*-substituted analogs.[22] Esters, nitriles, tertiary amines, (thio)ethers, bromides, protected aldehydes, trifluoromethoxy, and silyl groups can be present in the nucleophile structure leaving the catalytic process unaffected.[23]

The reaction can be easily scaled up to a gram scale. As such, the compound **1ah** was obtained in 91% yield and 98% *ee* on a 5 mmol scale (1.5 g of the starting benzyl bromide). Additionally, the reaction is not limited to benzylic electrophiles. Aliphatic α-CF_3-alkyl bromides undergo an efficient transformation under similar conditions, providing the product **4** in 91% yield and 95% *ee*. Moreover, aryltitanates can be prepared *in situ* starting from the corresponding aryl iodides via halogen−magnesium exchange with iPrMgCl·LiCl and further transmetalation to $Ti(OiPr)_4$ without significant effect on the reaction outcome (**1al** and **1am**; see SI for details).

Interestingly, benzyl *chlorides* also can be efficiently utilized in the reaction, yet in somewhat lower yields. As such, α-CF_3-4-chlorobenzyl chloride **2a′** was converted to the corresponding benzhydryl **1a** under similar reaction conditions in a 79% yield and 97% *ee* (Scheme 5).

Scheme 5. Cross-coupling of α-CF_3-Benzyl Chlorides

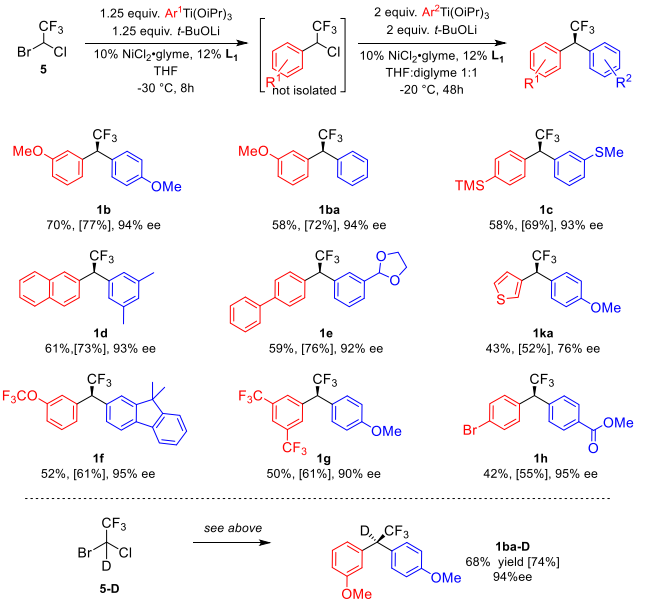


The unexpectedly high reactivity of α-CF_3-benzyl chlorides led us to explore another approach toward synthesis of compounds of family **1**. We envisioned that starting from 1-chloro-1-bromo-2,2,2-trifluoroethane, or halothane—a cheap commercially available anesthetic—it is possible to perform a sequential one-pot cross-coupling reaction[24] to prepare benzyl chlorides *in situ* followed by their conversion to **1**. If viable, the use of such a starting material in the catalytic asymmetric cross-coupling protocol would allow for the creation of α-CF_3-diarylmethanes through a rapid increase of a molecular complexity.

Gratifyingly, halothane undergoes a smooth reaction to provide the corresponding α-CF_3-benzyl chloride in a nearly quantitative yield under similar conditions. Moreover, both steps can be performed as a one-pot sequence without addition of extra amounts of the catalyst in the second step.[25]

Regarding the scope, we were pleased to see that this strategy allows for the creation of a variety of enantioenriched diarylmethanes (Scheme 6). The preparation of diaryltrifluoroethanes bearing both electron-rich and electron-poor aromatic motifs in any combination is feasible under the designed protocol. Generally, high yields are obtained if aryl titanates bearing electron-donating substituents are employed on each reaction step (**1b**). However, the use of less electron-rich coupling partners results in a yield decrease regardless of the stage of employment. As such, the use of electron-poor aryltitanates on the first step of the sequence affects the

Scheme 6. Scope of a One-Pot Sequential Cross-Coupling Reaction[a]



[a]Reactions were performed on 0.5 mmol scale in duplicate. Isolated yields are given. NMR yields are given in square brackets.

selectivity of the reaction, giving rise to the formation of the undesired symmetrical benzhydryl. The attempts to introduce an aryl moiety bearing electron-poor substituents on the second step increases amounts of product of formal dechlorodefluorination. Thus, compounds containing two electron-poor aryls are obtained only in moderate yields (**1h**). Additionally, this approach allows for a facile creation of deuterium-labeled analogues of this family of compounds (**1ba-D**) using easy-to-prepare halothane-D (**5-D**).

In conclusion, we have developed a method for the preparation of α-CF_3-substituted benzhydryls via an enantioselective nickel-catalyzed cross-coupling reaction. The use of an aryltitanate-based nucleophile enabled the synthesis of a variety of a chiral 1,1-diaryl-2,2,2-trifluoroethanes starting from α-CF_3-benzyl bromides in high yields and excellent enantioselectivities. Remarkably, our approach allows this reaction to be performed with electronically diverse electrophiles and nucleophiles including those bearing electron-donating substituents. Alternatively, the same family of products can be obtained under similar conditions as a one-pot two-step sequence starting from a cheap, commercially available anesthetic halothane in good yields and excellent enantioselectivities. To the best of our knowledge, it represents the first use of halothane as a CF_3-group donor in asymmetric catalysis. Mechanistic studies of aryltitanium involved asymmetric cross-coupling reactions are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03673.

Experimental procedures, characterization data, nuclear magnetic resonance and high performance liquid chromatography spectra of new compounds (PDF)

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Accession Codes

CCDC 2026395−2026396 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(17) Fu et al. presented a nickel-catalyzed Negishi cross-coupling reaction of aliphatic α-CF3-substituted electrophiles, yet the corresponding benzylic electrophiles were not shown to be suitable reaction partners. See refs 16k and 16l.
(18) While the exact reason of this improvement is currently under investigation, we speculate that the increase in an ionic strength of a solution due to the formation of soluble LiBr as a coproduct might be responsible for the improvement, allowing for more selective transmetalation. See ref 16k for a similar effect.
(19) **1a** was obtained in 56% yield (98% *ee*) and 60% yield (97% *ee*) in the reaction of **2a** with 3-methoxyphenylmagnesium bromide or 3-methoxyphenylzinc iodide correspondingly.
(20) The reaction is proposed to proceed via Ni(I)/Ni(III) catalytic cycle. No dynamic kinetic resolution of the electrophile was observed; the *ee* of the product remains constant during the course of the reaction. The reaction is interrupted with subequimolar amounts of TEMPO and resumes once it is consumed.
(21) 2-Thienyl or 2-furyl-derived electrophiles under similar conditions provided a complex mixture of products.
(22) *ortho*-Fluoro, -methyl, and -methoxy aryltitanium nucleophiles provided products in poor yields and/or enantioselectivities.
(23) The use of heteroaromatic aryltitanates, such as 2-thienyl and 6-methoxy-3-pyridyl, was unsucessful.
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(25) See Tables S1 and S2 for optimization of the reaction conditions and influence of conditions on the reaction outcome for the first and the second step of the cross-couipling reaction correspondingly.

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