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To be cited as: *Chem. Eur. J.* 10.1002/chem.201705463

Link to VoR: http://dx.doi.org/10.1002/chem.201705463

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10.1002/chem.201705463

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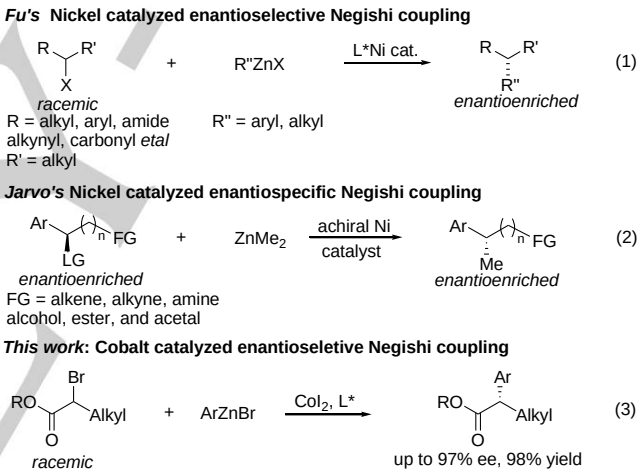
Cobalt-Catalyzed Enantioselective Negishi Cross-Coupling of Racemic α-Bromo Esters with Arylzincs

Feipeng Liu,[a] Jiangchun Zhong,[a] Yun Zhou,[a] Zidong Gao,[a] Patrick J. Walsh,[b] Xueyang Wang,[a] Sijie Ma,[a] Shicong Hou,[a] Shangzhong Liu,[a] Minan Wang,[a] Min Wang,[a] Qinghua Bian*[a]

Abstract: The first cobalt-catalyzed enantioselective Negishi cross-coupling reaction, and the first arylation of α-halo esters with arylzinc halides, are disclosed. Employing a cobalt-bisoxazoline catalyst, various α-arylalkanoic esters were synthesized in excellent enantioselectivities and yields (up to 97% ee and 98% yield). A diverse range of functional groups, including ether, halide, thioether, silyl, amine, ester, acetal, amide, olefin and heteroaromatics is tolerated by this method. This method was suitable for gram-scale reactions, enabling the synthesis of (*R*)-xanthorrhizol with high enantiopurity. Radical clock experiments support the intermediacy of radicals.

Transition-metal-catalyzed enantioselective cross-coupling reactions between alkyl electrophiles and organometallic nucleophiles, such as organozinc,[1] organoboron,[2] Grignard[3] and organosilane reagents,[4] have emerged as powerful tools for the construction of tertiary and quaternary stereogenic centers. Among these reactions, the Negishi cross-coupling of organozinc reagents exhibits exceptional functional group tolerance. As a result, significant progress has been made in broadening the scope of this powerful reaction, including the use of sp^3 hybridized electrophiles.[5] In the realm of enantioselective Negishi reactions, remarkable progress has been made by Fu and co-workers using enantioenriched nickel catalysts and racemic sp^3 hybridized electrophiles [Scheme 1, Eq. (1)].[1] In a complementary approach, enantiospecific Negishi reactions have been introduced by Jarvo and coworkers, as illustrated in the conversion of enantioenriched alkyl esters and ethers with preservation of enantiopurity [Scheme 1, Eq. (2)].[6]

The inexpensive and environmentally benign nature of cobalt has led to the development of cobalt-catalyzed Negishi cross-coupling reactions as valuable alternatives to the use of noble metal catalysts.[7] Despite the spectacular success of cobalt catalyzed cross-coupling reactions between alkyl halides and arylzinc reagents by Knochel and co-workers,[7e,f] no cobalt-catalyzed enantioselective Negishi cross-coupling reactions have been reported. We recently reported the first enantioselective Kumada cross-coupling reaction catalyzed by (bisoxazoline)Co complexes.[3o] To devise a more functional group tolerant synthesis of α-arylalkanoic acids, which are an important class of nonsteroidal anti-inflammatory drugs (NSAIDs),[8] we herein report the first cobalt-catalyzed asymmetric Negishi cross-coupling to generate α-arylalkanoic acids derivatives [Scheme 1, Eq. (3)]. This reaction enables the previously unrealized coupling of α-halo esters with arylzinc halides. We demonstrate this coupling's utility and scalability in the synthesis of (*R*)-xanthorrhizol and provide preliminary mechanistic investigations.



Scheme 1. Transition-metal-catalyzed enantioselective and enantiospececific Negishi cross-coupling reactions.

We initially surveyed chiral ligands in the enantioselective cross-coupling of racemic benzyl α-bromopropanoate **1a** with phenylzinc bromide **2a** (Table 1). The phenyl, isopropyl and isobutyl substituted bisoxazoline ligands **L1**–**L3** exhibited poor enantioselectivities (31–61%). In contrast, the benzyl-substituted bisoxazoline ligand (**L4**) exhibited high yield (93%) and enantioselectivity (90%). To search for a more efficient catalyst for this stereoconvergent cross-coupling, the methyl groups on the ligand backbone were replaced with hydrogens (**L5**), isobutyl (**L6**) and benzyl (**L7**) groups. Unfortunately, the enantioselectivities did not exceed those of the parent **L4**. We next modified the backbone benzyl groups of **L7**. Our bisoxazoline ligands (**L8**–**L14**) bearing either electron-donating or electron-withdrawing groups were more effective (84–92% ee) than the parent **L7**, and 4-fluorobenzyl bisoxazoline **L9** exhibited excellent yield (94%) and enantioselectivity (92%). The effect of other reaction parameters was elaborated in Tables S1 and S2 (see Supporting Information). The optimized reaction conditions involved 1.0 equiv of benzyl α-bromopropanoate and

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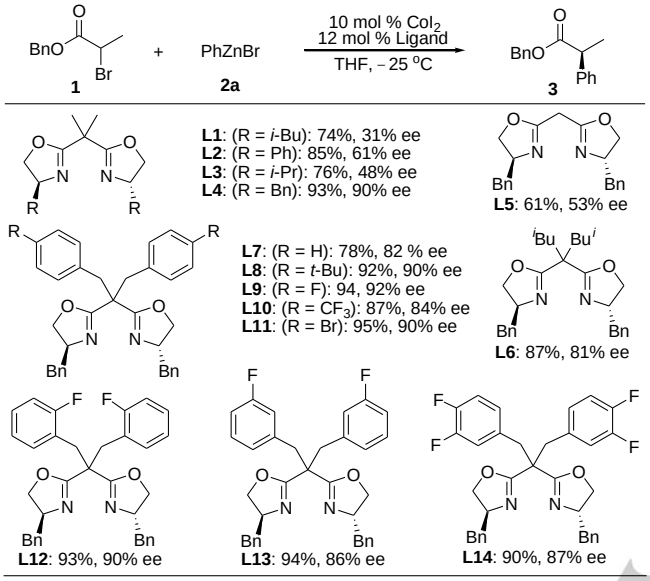
10.1002/chem.201705463

2.0 equiv of phenylzinc bromide at –25 °C in THF, catalyzed by 10 mol% CoI_2 and 12 mol% bisoxazoline **L9** (entry 11, Table S1 in Supporting Information). Based on comparison with reported specific rotations, the absolute configuration of the cross-coupling product **3a** was (*S*).[3o,9]

Table 1. Ligands screening for the enantioselective Negishi cross-coupling reaction.[a]

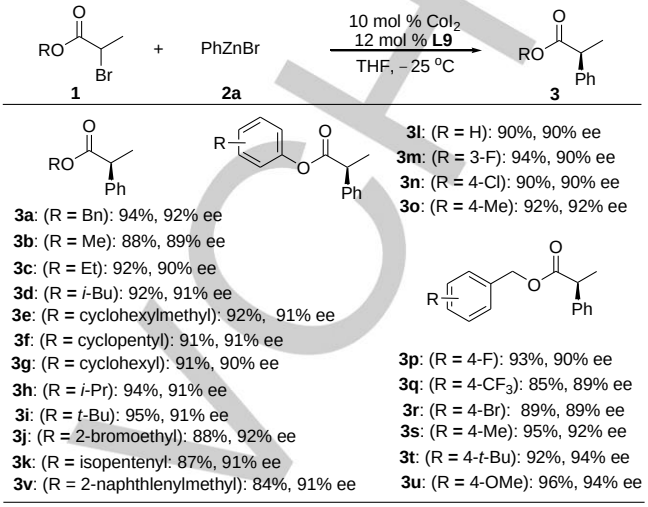


[a] All reactions were run for 24 h, and conducted on 0.5 mmol scale. 2.0 Equiv of PhZnBr was used. Isolated yields after chromatographic purification. Ee were determined by chiral HPLC.

Under the optimized conditions, the coupling reaction between *rac*emic α-bromo propionic esters bearing a variety of ester O–R groups and phenylzinc bromide were examined (Table 2). The reaction proved remarkably tolerant of the size and nature of the O–R group. Thus, α-bromo propionic esters with O–R substituents methyl (**3b**), ethyl (**3c**), *iso*-butyl (**3d**), and cyclohexylmethyl (**3e**) to more hindered cyclopentyl (**3f**), cyclohexyl (**3g**), *iso*-propyl (**3h**), and even bulky *tert*-butyl (**3i**) reliably exhibited excellent enantioselectivities (89–92%) and high yields (88–95%). Likewise, α-bromo propionic esters with functional groups, including alkyl bromide (**3j**), olefin (**3k**), phenyl (**3l**), benzyl (**3a**), and naphthalenylmethyl (**3v**), were very good substrates for this stereoconvergent arylation (90–92% ee, 84–94% yield). The nature of the substituent on the O–Ar group had little impact on the product enantioselectivity (90–94% ee, **3m**–**3u**), and the best results (94% ee, 96% yield, **3u**) were obtained with 4-methoxybenzyl 2-bromopropanoate (**1u**).

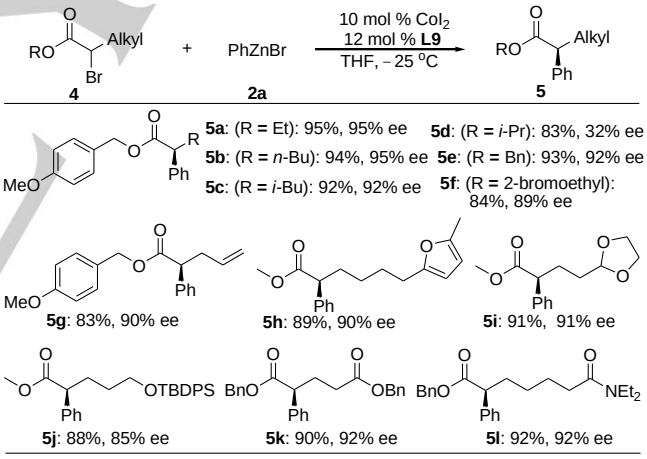
We next explored the use of different alkyl groups attached to the α-carbon of the bromo ester substrates (Table 3). When the α-alkyl was primary (Et, *n*-Bu, *i*-Bu), 92–95% ee and 92–95% yield were obtained (**5a**–**5c**). However, in the case of the bulky *iso*-propyl group, the cross-coupling product **5d** was generated in only 32% ee. Gratifyingly, α-bromo esters bearing functionalized alkyl groups, such as benzyl (**5e**), allyl (**5g**), acetal (**5i**), silyloxy (**5j**), ester (**5k**) and amide (**5l**), exhibited high enantioselectivities (85–92%) and 83–93% yield. The α-bromo ester containing a primary alkyl bromide underwent coupling with excellent chemoselectivity for the α-position, leading to **5f** with 89% ee and 84% yield. Likewise, use of ester bearing heterocycle 2-(5-methyl)furyl led to cross-coupling in 90% ee and 89% yield of **5h**.

Table 2. Enantioselective Negishi cross-coupling reactions of racemic α-bromo propionic esters with phenylzinc bromide.[a]



[a] All reactions were run for 24 h, and conducted on 0.5 mmol scale. 2.0 Equiv of PhZnBr was used. Isolated yields after chromatographic purification. Ee were determined by chiral HPLC.

Table 3. Enantioselective Negishi cross-coupling reactions of racemic α-bromo esters with phenylzinc bromide.[a]



[a] All reactions were run for 24 h, and conducted on 0.5 mmol scale. 2.0 Equiv of PhZnBr was used. Isolated yields after chromatographic purification. Ee were determined by chiral HPLC.

In addition to phenylzinc bromide, a wide array of arylzinc reagents successfully participated in this stereoconvergent coupling (Table 4). In general, electron-neutral and donating groups on the aryl ring (3-Me, 4-Me, 4-OMe, 4-*iso*-Bu, 4-Ph, 4-$SiMe_3$, 4-SMe, 4-NMe_2, 6-OMe) or electron-with drawing substituents (3-OMe, 3-OMe-4-Me, 3-F, 4-F, 4-CF_3, 3-Cl, 4-Cl, 4-CO_2Et, 3,4-F_2, 3,5-F_2, 3-Cl-4-F) on the aryl zinc uniformly afforded the cross-coupling products with excellent enantioselectivities (86–97%) and high yields (85–98%, **6b**–**6t**, **6v**). Notably, α-aryl propionic esters **6g** and **6v** could be transformed into two well known nonsteroidal anti-inflammatory drugs (NSAIDs), (*S*)-ibuprofen and (*S*)-naproxen, with high enantiomeric purity via simple deprotection and recrystallization.[3p,10] Our stereoconvergent arylation was

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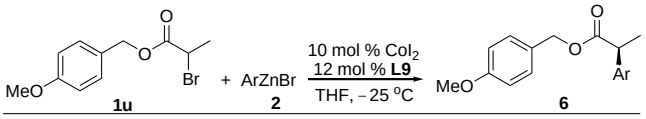
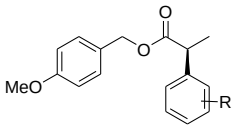
compatible with other functional groups, including acetal (**6y**) and heteroaromatics (**6w**, **6x**, **6z**, and **6za**). Furthermore, halogenated arylzinc reagents coupled smoothly with α-bromo ester **1u** indicating that this enantioselective coupling occurred with high chemoselectivity at the sp^3 C−Br bond. It is noteworthy that our method tolerated hindered substrates, and some *ortho*-substituted arylzinc reagents reacted smoothly with excellent enantioselectivities (87–88% ee) and yields (88–94%, **6zb**–**6ze**).

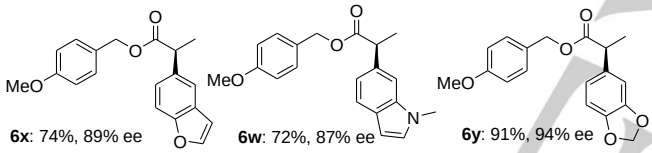
Table 4. Enantioselective Negishi cross-coupling reactions of racemic α-bromo ester with arylzinc bromide.[a]



6b: (R = 3-Me): 92%, 91% ee
6c: (R = 4-Me): 95%, 94% ee
6d: (R = 3-MeO): 92%, 92% ee
6e: (R = 4-MeO): 94%, 94% ee
6f: (R = 3-MeO, 4-Me): 94%, 92% ee

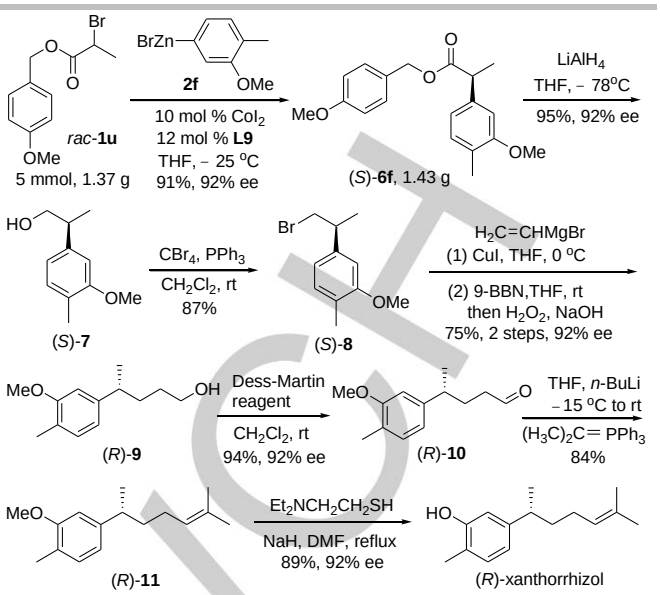


6g: (R = 4-*i*-Bu): 90%, 93% ee
6h: (R = 3-F): 94%, 92% ee
6i: (R = 4-F): 97%, 95% ee
6j: (R = 3,4-F_2): 98%, 97% ee
6k: (R = 3,5-F_2): 92%, 86% ee[b]
6l: (R = 4-CF_3): 88%, 94% ee
6m: (R = 3-Cl-4-F): 97%, 95% ee
6n: (R = 3-Cl): 92%, 92% ee
6o: (R = 4-Cl): 95%, 94% ee
6p: (R = 4-Ph): 92%, 92% ee
6q: (R = 4-$SiMe_3$): 92%, 92% ee
6r: (R = 4-SMe): 85%, 92% ee
6s: (R = NMe_2): 86%, 92% ee
6t: (R = 4-COOEt): 85%, 93% ee[b]
6u: (R = 2-naphthlenyl): 91%, 89% ee
6v: (R = 6'-MeO-2-naphthyl): 83%, 89% ee
6z: (R = 4-pyrrolyl): 89%, 93% ee
6za: (R = 4-thienyl): 83%, 92% ee
6zb: (R = 2-Me): 93%, 87% ee[c]
6zc: (R = 2,4-Me_2): 90%, 87% ee[c]
6zd: (R = 2-OMeI): 94%, 88% ee[c]
6ze: (R = 1-naphthyl): 88%, 87% ee[c]



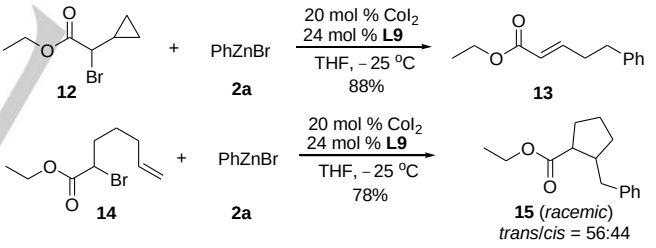
[a] All reactions were run for 24 h, and conducted on 0.5 mmol scale. 2.0 Equiv of ArZnBr was used. Isolated yields after chromatographic purification. Ee were determined by chiral HPLC. [b] 5.0 Equiv of ArZnBr was used. [c] Ligand **L4** and 3.0 equiv of ArZnBr were used.

To demonstrate the scalability and utility of our method, (*R*)-xanthorrhizol was prepared (Scheme 2). (*R*)-Xanthorrhizol is a sesquiterpene isolated from *Curcuma xanthorrhiza* Roxb. Rhizome,[11] and has anti-inflammatory, antioxidant, and antiestrogenic properties.[12] The synthesis started from coupling of racemic 4-methoxybenzyl 2-bromopropanoate (**1u**, 5 mmol, 1.37 g) to generate the arylated product (*S*)-**6f** (1.43 g, 91% yield, 92% ee). Subsequent reduction with $LiAlH_4$[4a] and bromination with carbon tetrabromide[13] afforded primary bromide (*S*)-**8**. After coupling with vinylmagnesium bromide,[14] hydroboration with 9-BBN and oxidation with basic H_2O_2 furnished primary alcohol (*R*)-**9** (92% ee, 75% yield over 2 steps).[15] Finally, Dess-Martin oxidation[16] and Wittig olefination with *iso*-propyltriphenylphosphonium iodide,[17] followed by cleavage of the methyl ether with 2-diethylaminoethanethiol and NaH gave (*R*)-xanthorrhizol with 92% ee.[18]



Scheme 2. Enantioselective synthesis of (*R*)-xanthorrhizol.

To gain insight into the mechanism of this cobalt-catalyzed reaction, radical probes **12** and **14** with phenylzinc bromide **2a** were examined (Scheme 3). The ring-opened product **13** was formed in 88% yield from α-bromo cyclopropyl ester **12**. In addition, the cyclized cross-coupling product **15** was obtained as a racemic mixture of diastereomers (78% yield, *trans:cis* = 56:44) from α-bromo ester **14** that bears pendant olefin. These results indicate that this cobalt-catalyzed cross-coupling process likely involves a radical pathway similar to cobalt-catalyzed cross-coupling reactions of alkyl halides.[19]



Scheme 3. Cobalt-catalyzed reaction of radical probes **12** and **14** with PhZnBr.

In conclusion, we have developed the first cobalt-catalyzed enantioselective Negishi cross-coupling reaction and the first arylation of α-halo esters with arylzinc halides. A diverse range of functionalized arylzinc reagents were successfully coupled with various α-bromo esters to afford enantioenriched α-arylalkanoic esters with high enantioselectivities and yields under mild conditions. In particular, ortho-substituted arylzinc reagents, which had not previously been successfully employed in asymmetric cross-coupling reactions with α-bromo esters,[3o,3p,4a] were excellent substrates. This stereoconvergent arylation could be readily conducted on gram-scale, as demonstrated in the enantioselective synthesis of (*R*)-xanthorrhizol. We expect that this cobalt-catalyzed asymmetric Negishi cross-coupling reaction will find further applications in medicinal chemistry.

Acknowledgements

We thank for the National Key Technology Research and Development Program of China (No. 2015BAK45B01 and 2017YFD0201404) for the financial support. PJW thanks the NSF (CHE-1464744).

Keywords: cobalt • Negishi cross-coupling• α-bromo ester • arylzinc • asymmetric catalysis

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10.1002/chem.201705463

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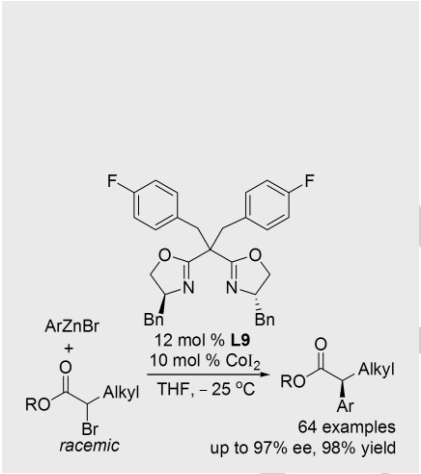
COMMUNICATION

The first cobalt-catalyzed enantioselective Negishi cross-coupling reaction and the first examples of arylation of α-halo esters with arylzinc halide, have been developed. Employing a cobalt-bisoxazoline catalyst, various α-arylalkanoic esters (64 examples) were synthesized in excellent enantioselectivity and yield (up to 97% ee and 98 % yield) from racemic α-bromo esters and arylzincs.



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