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Transmetal-Catalyzed Enantioselective Cross-Coupling Reaction of Racemic Secondary Benzylic Bromides with Organoaluminum Reagents

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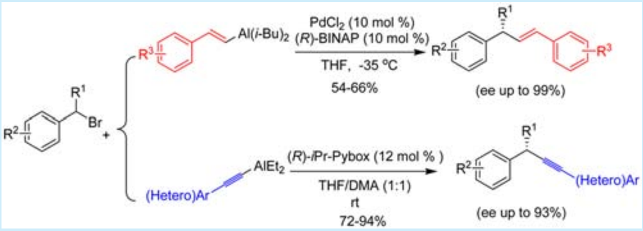
Supporting Information

ABSTRACT: The transmetal-catalyzed enantioselective cross-coupling reaction of secondary benzylic electrophiles with organoaluminum reagents has been developed. The reaction of secondary benzylic electrophiles with alkynylaluminum reagents provides a mild way for the chiral propargyl compounds bearing aromatic group in high yields with good enantioselectivities using $NiBr_2$·diglyme and (*R*)-*i*Pr-Pybox as the catalytic system. The reaction of secondary benzylic electrophiles with alkenylaluminum reagents affords the corresponding chiral aryl alkenes in moderate yields with excellent stereoselectivities using commercially available $PdCl_2$ and (*R*)-BINAP as the catalytic system.



In the past decade, palladium- and nickel-catalyzed cross-coupling reactions of secondary alkyl electrophiles bearing *β*-hydrogens have benefitted from significant progress,[1] namely, the groundbreaking studies on Negishi reactions of primary alkyl bromides and iodides with a range of organozinc reagents catalyzed by the nickel complexes.[2] Recently, Fu and co-workers have further championed an array of transmetal-catalyzed asymmetric cross-coupling reaction[3] of various secondary alkyl electrophiles with organozincs,[4] -borons,[5] -silicons,[6] and aryl Grignard reagents.[7] Compared with the asymmetric cross-coupling reactions of aryl nucleophiles, fewer examples of the asymmetric cross-coupling reactions of alkenyl and alkynyl nucleophiles were reported. For alkenyl nucleophiles, Fu and co-workers reported a sole nickel-catalyzed enantioselective cross-coupling reaction of racemic *α*-bromoketones with alkenylsilanes and alkenylzirconium reagents.[6,8] For alkynyl nucleophiles, only one example of the asymmetric alkynylation of alkyl electrophiles through the cross-coupling reaction of alkynyl indiums with racemic benzyl bromides was reported.[9] Alkynes and alkenes are extremely versatile functional groups; therefore, the development of the asymmetric cross-coupling reactions of alkenyl and alkynyl nucleophiles is attractive.

Organoaluminum nucleophiles have been widely applied in asymmetric addition to carbonyl compounds[10] and cross-coupling reactions,[11] due to the high reactivity and Lewis acidity of the aluminum center. Recently, cross-coupling reactions of aluminum acetylide with benzylic bromides catalyzed by $NiCl_2(PPh_3)_2$ have also been reported.[12] However, the organoaluminum nucleophiles for asymmetric cross-coupling reactions remains to be disclosed. Herein, we will report the first example of enantioselective cross-coupling reaction of secondary benzylic bromides with alkenyl- or alkynylaluminum reagents.

The asymmetric cross-coupling reaction of *α*-methyl benzyl bromide **1a** with alkynyldiethylaluminum **2a** was used as the template reaction to screen different chiral ligands (Figure 1), and the results are summarized in Table 1. First, chiral bidentate phosphine $\mathbf{L_1}$ or phosphoramidite ligands $\mathbf{L_2}$−$\mathbf{L_4}$ gave disappointing results with trace product formation (Table 1, entries 1−4). The reaction employing $NiBr_2$·diglyme with the (diphenylphosphino)phenyl substituted chiral oxazoline $\mathbf{L_5}$−$\mathbf{L_6}$ afforded the coupling product **3a** in moderate yields with low enantioselectivities (Table 1, entries 5−6). Next, we examined the chiral bis(oxazoline) ligand $\mathbf{L_7}$ (Table 1, entry 7) and Pybox $\mathbf{L_8}$−$\mathbf{L_{12}}$ (Table 1, entries 8−12) for the asymmetric cross-coupling reactions. Results are consistent with the asymmetric

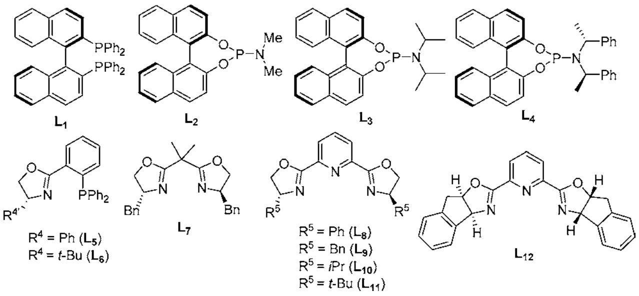


Figure 1. Different chiral ligands.

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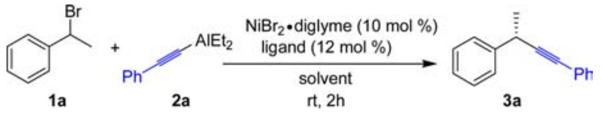
Table 1. Optimization for Nickel-Catalyzed Cross-Coupling Reaction of α-Methyl Benzylbromide 1a with Alkynyldiethylaluminum 2a[a]

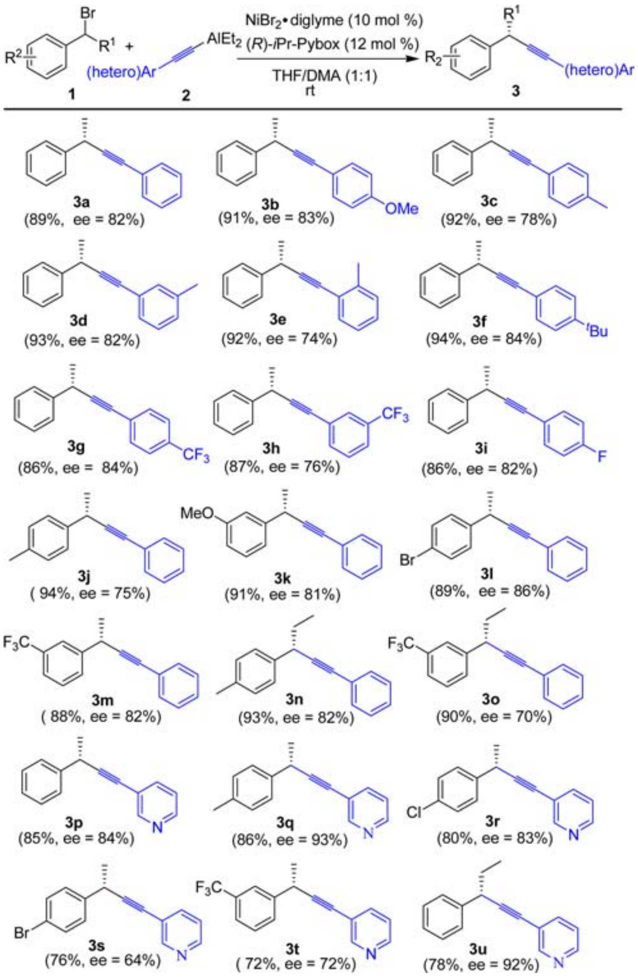


entry	ligand (mol %)	solvent	yield (%)[b]	ee (%)[c]
1	**L$_1$** (12)	THF	trace	
2	**L$_2$** (12)	THF	trace	
3	**L$_3$** (12)	THF	trace	
4	**L$_4$** (12)	THF	trace	
5	**L$_5$** (12)	THF	61	8
6	**L$_6$** (12)	THF	34	rac
7	**L$_7$** (12)	THF	73	24
8	**L$_8$** (12)	THF	80	14
9	**L$_9$** (12)	THF	82	18
10	**L$_{10}$** (12)	THF	85	50
11	**L$_{11}$** (12)	THF	85	30
12	**L$_{12}$** (12)	THF	63	15
13[d]	**L$_{10}$** (12)	THF	trace	
14[e]	**L$_{10}$** (12)	THF	52	rac
15[f]	**L$_{10}$** (12)	THF	70	10
16	**L$_{10}$** (12)	*n*-hexane	trace	
17	**L$_{10}$** (12)	CH_2Cl_2	11	2
18	**L$_{10}$** (12)	Et_2O	8	
19	**L$_{10}$** (12)	DME	trace	
20	**L$_{10}$** (12)	DMA	83	75
21	**L$_{10}$** (12)	THF/DMA (1:1)	89	82
22	**L$_{10}$** (10)	THF/DMA (1:1)	84	76
23	**L$_{10}$** (15)	THF/DMA (1:1)	88	82
24[g]	**L$_{10}$** (12)	THF/DMA (1:1)	89	81
25[h]	**L$_{10}$** (12)	THF/DMA (1:1)	80	76

[a] Conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), solvent (10.0 mL). [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC analysis. [d] Employing 10 mol % $CuCl_2$. [e] Employing 10 mol % $PdCl_2$. [f] Employing 10 mol % $NiCl_2$·diglyme. [g] 1.8 equiv of **2a** was used. [h] 1.2 equiv of **2a** was used.

cross-coupling reactions of secondary benzyl bromides and trialkynylindium reagents,[9] and the best catalytic system was $NiBr_2$·diglyme and (*R*)-*i*Pr-Pybox to afford the product **3a** in 85% yield with 50% ee (Table 1, entry 10). The use of other metal catalysts did not improve the yield and enantioselectivity (Table 1, entries 13−15). When the reaction was performed by using $NiBr_2$·diglyme and (*R*)-*i*Pr-Pybox in a 1:1 mixed solvent of DMA/THF (DMA = dimethylacetamide), the yield of the coupling product rose up to 89% with good enantioselectivity of 82% ee (Table 1, entry 21). Further optimization of the loadings of chiral ligand **L$_{10}$** and the equivalents of **2a** did not improve the enantioselectivity (Table 1, entries 22−25).

Scheme 1. Substrate Scope for Nickel-Catalyzed Cross-Coupling Reaction of Benzylic Bromides with Alkynyldiethylaluminum Reagents[a,b]

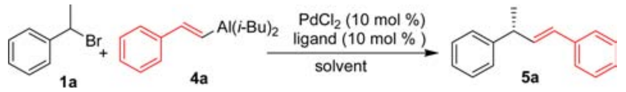


[a] Conditions: **1** (0.5 mmol), **2** (0.75 mmol), DMA/THF (10.0 mL). [b] The absolute configuration of **3a** was assigned by comparison of the specific rotation value in ref 9, and those of other products were assigned by analogy.

With the optimized reaction conditions established, we extended the reaction to various alkynyldiethylaluminum reagents and various benzyl bromide (Scheme 1). The catalytic system works well to various alkynyldiethylaluminum reagents bearing either electron-donating or electron-withdrawing substituents. Reaction of α-methylbenzyl bromide **1a** with alkynyldiethylaluminum reagents gives the corresponding coupling products **3a**−**3i** in high yields with good enantioselectivities (86−94% yield, 74−84% ee). Furthermore, the reaction of other benzylic substrates with phenylethynyl aluminum reagents was examined, results showed the corresponding coupling products **3j**−**3m** in high yields with good enantioselectivities. Notably, the substrate containing a methoxy group was well-tolerated in the reaction to give the product **3k**. However, the benzylic bromide bearing an amide group was not a suitable substrate. Reaction with α-ethylbenzyl bromide also gave the corresponding coupling products **3n** and **3o** in high yields with good enantioselectivities. It was noteworthy that the reaction of alkynyldiethylaluminum reagents bearing pyridyl group could also work well to afford the chiral propargyl compounds **3p**−**3u** in good yields with good to high enantioselectivities of up to 93% ee. Unfortunately, aliphatic hexyn-1-yl or trimethylsilylethynyl aluminum reagents were not tolerated in the reaction.

In order to further develop the organoaluminum nucleophiles for asymmetric cross-coupling reaction, we further tested the cross-coupling reaction of α-methyl benzyl bromide **1a** with alkenylaluminum reagent **4a** using $NiBr_2$·diglyme and (*R*)-*i*Pr-Pybox as the catalytic system. Unfortunately, under the same conditions the secondary benzyl electrophiles were not able to efficiently cross-couple with alkenylaluminum reagent. Recently, Pd-catalyzed stereospecific allyl−aryl coupling reactions of enantioenriched allylic electrophiles with arylboronic acids afforded structurally diverse alkenes in good yields with perfect retention of ee, indicating Pd-catalyzed controllable stereospecific cross-coupling reactions.[13] So, we tested the cross-coupling reaction of the secondary benzyl electrophiles with alkenylaluminum reagents employing a palladium catalyst. $PdCl_2$ and different ligands were first examined for cross-coupling reaction of alkenylaluminum reagents (Table 2, entries 1−5), and results showed that $PdCl_2$ and (*R*)-BINAP was the appropriate catalytic system to afford the product **5a** in 80 yield with 60% ee (Table 2, entry 1). Decreasing reaction temperature to −35 °C improved the results to give **5a** in 58% yield with 88% ee (Table 2, entry 7). Further optimization of the different palladium catalyst, we did not obtain the desired product in the satisfactory yield or enantioselectivity (Table 2, entries 10 and 11).

Table 2. Optimization for Palladium-Catalyzed Cross-Coupling Reaction of *α*-Methyl Benzyl Bromide 1a with Alkenylaluminum Reagent 4a[a]



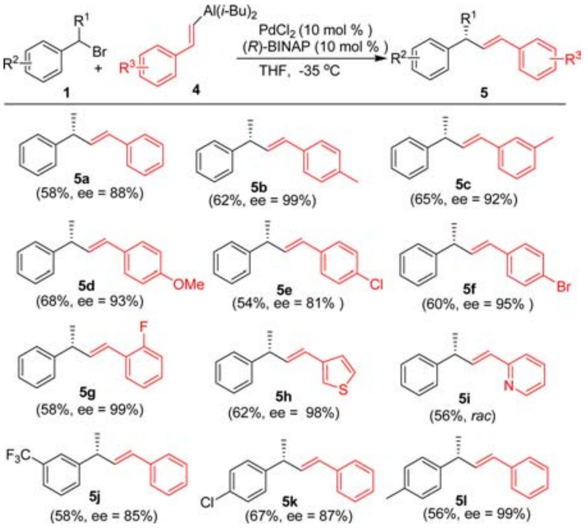
entry	ligand	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	L_1	THF	rt	6	80	60
2	L_2	THF	rt	6	92	20
3	L_4	THF	rt	6	90	25
4	L_8	THF	rt	6	trace	
5	L_{12}	THF	rt	6	trace	
6	L_1	THF	0	12	78	61
7	L_1	THF	−35	48	58	88
8	L_1	toluene	−35	48	50	79
9	L_1	*n*-hexane	−35	48	trace	
10[d]	L_1	THF	−35	48	55	8
11[e]	L_1	THF	−35	48	50	71

[a]Conditions: **1a** (0.5 mmol), **4a** (0.75 mmol), solvent (10.0 mL). [b]Isolated yield. [c]The enantiomeric excess was determined by HPLC analysis. [d]Employing 10 mol % $Pd(\eta^3\text{-}C_5H_3)_2Cl_2$. [e]Employing 10 mol % $Pd(CH_3CN)_2Cl_2$.

With the optimized reaction conditions established, we extended the reaction to various alkenylaluminum reagents and benzyl bromides (Scheme 2). As illustrated in Table 4, the catalytic system works well to various alkenylaluminum reagents bearing either electron-donating or electron-withdrawing substituents to afford the corresponding coupling products **5a**−**5g** in moderate yields with excellent enantioselectivities except for 4-chlorophenylethynyl aluminum to afford product **5e** in 81% ee. The cross-coupling reaction of *α*-methyl benzyl bromide **1a** with 3-thienyl vinylaluminum afforded the corresponding product **5h** in 98% ee; however, reaction with 2-pyridylethenylaluminum afforded the *racemic* product **5i**, probably due to coordination of heteroatom. Further, the cross-coupling reaction of different benzyl bromides also provided the corresponding products **5j**−**5k** in moderate yields with good to excellent enantioselectivities. An aliphatic 1-hexenyldiisobutylaluminum reagent is not suitable for the reaction.

Based on previous relevant studies on Ni- and Pd-catalyzed cross-couplings of benzylic halides with other organometallic reagents,[14] after formation of the M−C bond via oxidative addition of benzylic bromide to *in situ* generated Ni(0) or Pd(0) species, two tentative pathways have been proposed to rationalize the stereoconvergence of such cross-couplings:[9] the adduct might undergo nucleophilic exchange with Ni(0) or Pd(0) species in the system or a rearrangement via planar benzylic metal species to form the most reactive or stable diastereoisomeric metal complex with the chiral ligand.

Scheme 2. Substrate Scope for Palladium-Catalyzed Cross-Coupling Reaction of Benzylic Bromides with Alkenylaluminum Reagents[a,b]



[a]Conditions: **1** (0.5 mmol), **4** (0.75 mmol) at −35 °C for 48 h in THF (10.0 mL). [b]The absolute configuration of **5a** was assigned by comparison of the specific rotation value in ref 13f, and those of other products were assigned by analogy.

In summary, we described the transmetal-catalyzed enantioselective cross-coupling reaction of secondary benzyl electrophiles with organoaluminum reagents. The reaction of secondary benzylic electrophiles with alkynylaluminum reagents provides the chiral internal alkynes bearing (hetero)-aromatic groups in high yields with good enantioselectivities using $NiBr_2$·diglyme and (*R*)-*i*Pr-Pybox as the catalytic system. It was noteworthy that the cross-coupling of secondary benzyl electrophiles with alkenylaluminum reagents affords the corresponding chiral aryl alkenes in moderate yields with excellent stereoselectivities of up to 99% ee employing the commercially available $PdCl_2$ and (*R*)-BINAP.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02933.

Experimental and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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