Cross-Coupling

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Intra- and Intermolecular Nickel-Catalyzed Reductive Cross-Electrophile Coupling Reactions of Benzylic Esters with Aryl Halides

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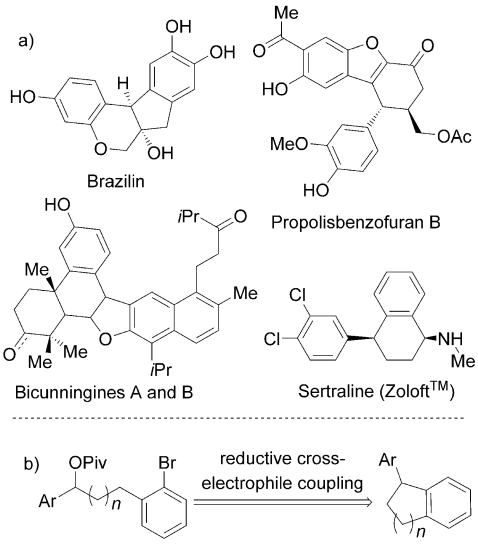
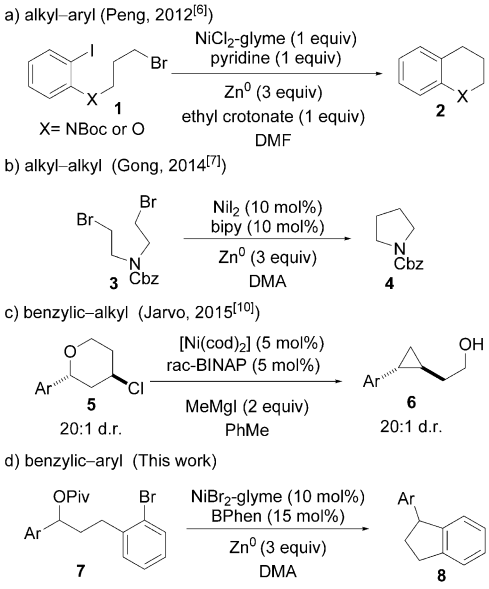
Abstract: *Nickel-catalyzed cross-electrophile coupling reactions of benzylic esters and aryl halides have been developed. Both inter- and intramolecular variants proceed under mild reaction conditions. A range of heterocycles and functional groups are tolerated under the reaction conditions. Additionally, the first example of a stereospecific cross-electrophile coupling of a secondary benzylic ester is described.*

Nickel-catalyzed reductive cross-electrophile coupling reactions have recently undergone rapid advances with respect to synthetic utility and mechanistic understanding.[1] Their mild reaction conditions can provide advantages to traditional cross-coupling reactions. For example, reductive coupling reactions offer an attractive strategy toward intramolecular cyclization reactions because they do not require installation of both electrophilic and organometallic functional groups into the starting material.[2] We envisioned a cross-electrophile reductive coupling reaction would provide straightforward synthesis of 1-arylindanes and tetralins, common motifs in natural products and pharmaceutical agents (Scheme 1).[3,4]

While intermolecular reductive coupling reactions have undergone rapid development in recent years,[1,5] few intramolecular variants have been reported. The group of Peng disclosed a stoichiometric nickel-catalyzed reductive coupling reaction to access nitrogen- and oxygen-containing heterocycles (Scheme 2a).[6] In 2014, Gong and co-workers reported a catalytic intramolecular cyclization of dihaloalkanes to access 5- and 6-membered rings (Scheme 2b).[7] Recently, much interest has focused on the use of C–O electrophiles in reductive coupling reactions.[1b,c,8,9] Our laboratory has reported a reductive ring-contraction of 4-chlorotetrahydropyrans to generate cyclopropanes (Scheme 2c).[10] To further expand the scope of intramolecular cross-electrophile coupling reactions, we targeted cyclization reactions of benzylic esters with aryl halides to afford valuable indanes and tetralins (Scheme 2d). These reactions would also complement recent efforts to develop intermolecular reductive coupling reactions to include alcohol derivatives.[11] Herein we report the intra- and intermolecular reductive cross-electrophile coupling reactions of benzylic pivalates with aryl halides and provide evidence for a stereospecific cyclization reaction.



Scheme 1. Intramolecular reductive cross-electrophile coupling reaction for synthesis of indanes and tetralins. Piv = pivaloyl.



Scheme 2. Nickel-catalyzed intramolecular reductive cross-electrophile coupling reactions. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide,

We designed the secondary benzylic pivalate **9** as a model substrate (see Table 1), based on our previous work in cross-coupling reactions of benzylic electrophiles.[12] These sub-

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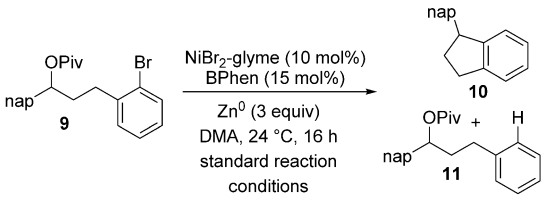
strates are easily prepared by lithiation of an arene and addition into the corresponding bromophenyl aldehyde. Additionally, benzylic pivalate esters are less reactive than their halide counterparts. Reaction of **9** in the presence of catalytic $NiBr_2$-glyme, bathophenanthroline (BPhen), and Zn^0 provided the desired product **10** in excellent yield with negligible yields of hydrodehalogenation (Table 1, entry 1).

Table 1: Optimization of reaction conditions.



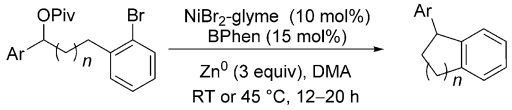
Entry	Variation from standard reaction conditions	Yield **9** [%][a]	**10** [%][a]	**11** [%][a]
1	none	<2	90	<2
2	Ac instead of Piv	59	9	13
3	Mn instead of Zn	80	<2	<2
4	dppf instead of BPhen	26	25	49
5	bipy instead of BPhen	20	42	25
6	terpyridine instead of BPhen	86	<2	<2
7	pybox instead of BPhen	98	<2	<2
8	no ligand	100	<2	<2
9	no $NiBr_2$-glyme	93	<2	<2
10	pyridine (40 mol%)	25	4	61
11	NaI (25 mol%)	<2	25	68
12	$NiCl_2$-glyme instead of $NiBr_2$-glyme	12	79	4
13	DMF instead of DMA	<2	44	35

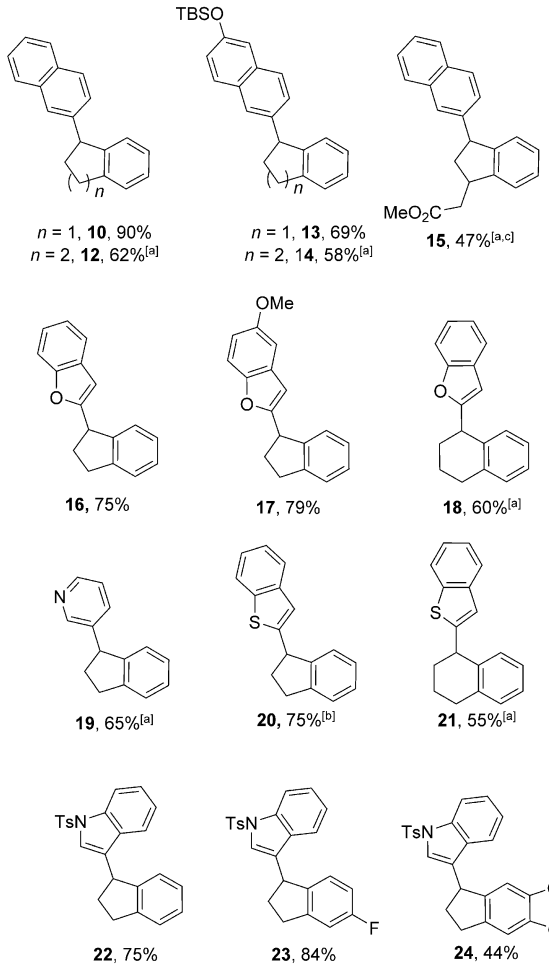
[a] Determined by ^{1}H NMR spectroscopy using PhTMS as an internal standard. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, TMS = trimethylsilyl.

Less sterically encumbered esters, such as acetate, provided lower conversion under the reaction conditions (entry 2). Alternative reducing agents such as Mn^0 also provided lower yields (entry 3). Utilizing phosphine and other aromatic nitrogen-containing ligands, such as bipy or pybox, resulted in a dramatic decrease in product formation (entries 4–7). In the absence of a ligand or a nickel catalyst, the desired cyclization does not occur (entries 8 and 9). Additives known to promote reactivity in other reductive cross-electrophile coupling reactions were also examined.[13] The addition of either pyridine or NaI favored hydrodehalogenation (entries 10 and 11).

Having established reaction conditions for the cyclization of the model substrate **9**, we set out to investigate the scope of the transformation (Table 2). Cyclization of a series of napthylic esters provides the tetralins **12** and **14**, which correspond to the core of bicunningines A and B[14] and the tetracyclic indanes **10**, **13**, and **15**. Benzofuran and benzothiophene moieties were well-tolerated, thus providing good yields for both indanes and tetralins (**16**–**18**, **20** and **21**). Additionally, substrates containing N-heterocycles were found to undergo the desired cyclization. The pyridine-substituted indane **19** can be synthesized in 65% yield and the

Table 2: Scope of the intramolecular cross-electrophile coupling.





Yield is that of the isolated product. [a] Reaction run with 15 mol% $NiBr_2$-glyme and 45 °C. [b] Reaction run at 45 °C. [c] Both starting material and product are 1:1 d.r. TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.

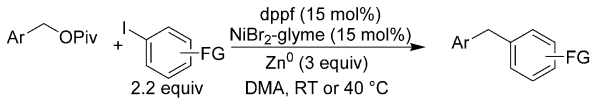
N-tosylindoles **22**–**24** were obtained in good yields. Substrates containing methoxy, fluoro, silyl, and ester substituents were also well-tolerated under the reaction conditions. Notably, these cyclization reactions proceed smoothly without the aid of a Thorpe–Ingold effect.[15]

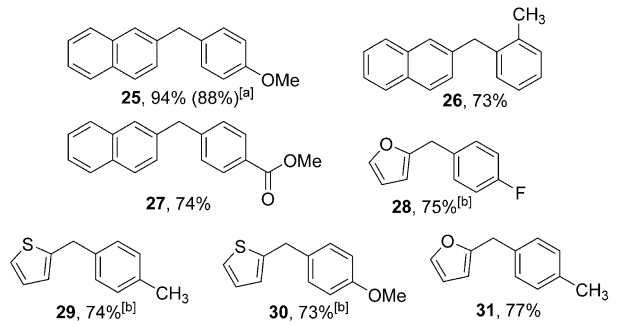
Next, we sought to determine whether these reaction conditions could be directly applied to an intermolecular variant of the cross-electrophile coupling reaction. With primary benzylic esters, this work would be complimentary to that of Weix and co-workers, forming similar diarylmethane products without the need of a cobalt cocatalyst.[9b] Implementation of our previous intramolecular coupling reaction conditions yielded minimal desired product, with dimerization of the benzylic electrophile being the major product (see the Supporting Information). Interestingly, switching the ligand to dppf increased the yield of the desired

diarylmethane to 98% and suppressed the formation of the dimer.[16]

With suitable reaction conditions identified, we examined the scope of the intermolecular cross-electrophile coupling reaction (Table 3). Coupling of naphthylic pivalates proceeded at room temperature in high yields (**25**–**27**). *Ortho*-substitution did not hinder desired reactivity, thus forming **26** in high yield. Iodobenzene derivatives containing aryl ether, methyl benzoate, and fluoro functional groups were also well-tolerated. Furyl- and thiophenyl-substituted pivalates provided high yields of diarylmethanes at slightly elevated temperatures (**28**–**31**).[17] Simple benzylic esters, for example, benzyl pivalate, were unreactive under the optimized reaction conditions even upon heating of the reaction mixture, as were indole- and pyridyl-substituted pivalates. Additionally, excess aryl iodide is observed upon workup and the desired reaction can proceed with as little as 1.1 equivalents of aryl iodide.

Table 3: Scope of intermolecular cross-electrophile coupling reaction.

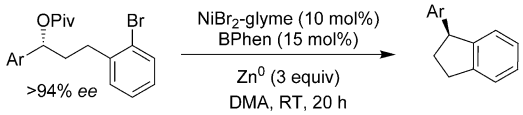


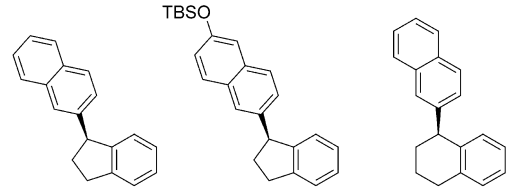


Yield is that of the isolated product. [a] Used 1.1 equiv of 4-iodoanisole. [b] Reaction run at 40 °C. FG = functional group.

Finally, we sought to determine whether the intramolecular cyclization could proceed in an enantiospecific fashion. While several examples of stereoconvergent reductive coupling reactions have been reported,[5a,9b,11b,13b,18] to the best of our knowledge, there is only one example of an enantiospecific reductive coupling reaction.[1b,c,8] Subjecting (*R*)-**9** to the optimized reaction conditions afforded (*S*)-**10** in 90% yield in 88% enantiomeric excess with 92% enantiospecificity (Table 4). Based on comparison of the data for (*S*)-**10** to the literature values, [19,20] the reductive cross-electrophile coupling reaction proceeds with inversion at the benzylic center. The indane (*S*)-**13** was also formed with high enantiospecificity, as was the tetralin (*S*)-**12**. Notably, all three of these substrates contain the napthylic ether moiety, which we hypothesize is prone to rapid and stereospecific oxidative addition reactions.[12] Substrates wherein the ester is activated by a heterocycle such as benzofuran, benzothiophene, or indole provided lower enantiospecificity.[21] This change in stereoselectivity likely correlates to a change in the reaction mechanism. Investigation of the mechanistic details is ongoing.

Table 4: Stereospecific cyclization.





Yield is that of the isolated product. The es value was determined by SFC.

In summary, the intramolecular reductive cyclization for the synthesis of indanes and tetralins has been developed. Additionally, the synthesis of diarylmethanes by an intermolecular cross-electrophile coupling of primary benzylic esters and aryl iodides is also described. The reactions are tolerant of a variety of heterocycles and functional groups. We have also demonstrated stereospecific cross-electrophile coupling reaction of benzylic esters for synthesis of enantioenriched 1-arylindanes and tetralins.

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[17] Addition of CoPc (1.5 mol%) improves the yield of **29** from 74 to 99%, although likely by changing the mechanism. In the presence of cobalt and the absence of nickel no reaction occurs. See the Supporting Information for details.
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[20] For complete details, see the Supporting Information.
[21] When enantioenriched starting materials were employed, the products **16**, **18**, **20**, and **23** were formed with less than 50% es. For details, see the Supporting Information.

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