Cross-Coupling

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Catalytic Asymmetric Cross-Couplings of Racemic α-Bromoketones with Arylzinc Reagents**

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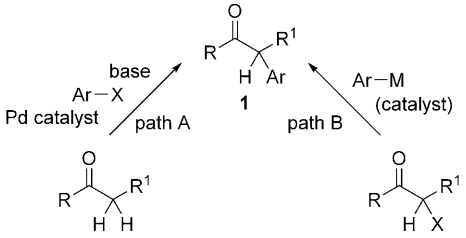
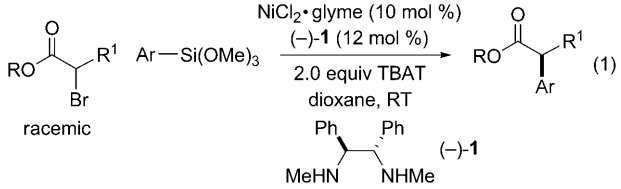
Many interesting target molecules include ketones that bear an α-aryl substituent, making the development of methods for the synthesis of this structural motif an active area of investigation.[1] For example, extensive efforts have recently been devoted to the discovery of palladium catalysts for the cross-coupling of ketones with aryl halides in the presence of a Brønsted base (path A in Scheme 1; through an enolate).[2]



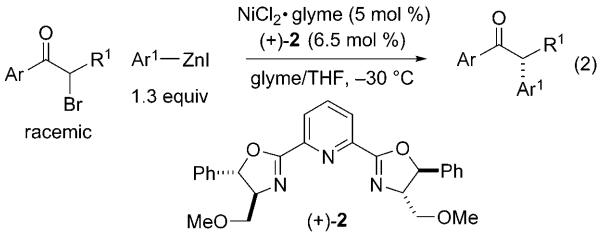
Scheme 1. Methods for synthesizing ketones having α-aryl substituents.

Furthermore, in the case of α,α-disubstituted ketones, catalytic asymmetric α-arylations have been described wherein quaternary stereocenters are generated with excellent enantioselectivity.[3,4] Unfortunately, these methods cannot be applied to the asymmetric synthesis of more commonly encountered tertiary stereocenters, because of the propensity of α-arylketones, such as **1**, to enolize under the reaction conditions.[5,6]

Alternatively, an umpolung arylation process, whereby a ketone bearing an α leaving group reacts with an arylmetal reagent, could provide the target α-arylketone (path B in Scheme 1). Until recently, there were no examples of palladium- or nickel-catalyzed cross-couplings between secondary α-halocarbonyl compounds and arylmetals (metal = B, Si, Sn, or Zn). In 2007, we reported that a nickel catalyst can achieve Hiyama arylation reactions with a wide array of electrophiles, including secondary α-halocarbonyl compounds, and Lei and co-workers later described a nickel-based method for Suzuki couplings.[7] In the case of α-haloesters, we were able to subsequently develop a catalytic asymmetric α-arylation process that furnished tertiary stereocenters [Eq. (1); TBAT = $[F_2SiPh_3]^-$ $[NBu_4]^+$].[8] However, we could not apply this method to corresponding Hiyama arylations of α-haloketones, presumably because of the Brønsted basic reaction conditions.[9,10]



Unlike cross-coupling processes such as the Hiyama and Suzuki reactions, which often employ Lewis or Brønsted basic activators, the Negishi reaction typically proceeds without an additive,[11,12] thereby making it an attractive starting point for the development of a method for the catalytic asymmetric α-arylation of ketones to generate (potentially labile) tertiary stereocenters. Herein, we establish that a nickel/pybox **2** catalyst can indeed achieve enantioselective cross-couplings of racemic α-bromoketones with arylzinc reagents under very mild conditions with a good *ee* value and yield [Eq. (2)].[13,14]



The data in Table 1 illustrate the role that various reaction parameters play in determining the efficiency of this stereoconvergent Negishi α-arylation of ketones. Cross-coupling does not occur if $NiCl_2$·glyme is omitted (Table 1, entry 2), whereas carbon–carbon bond formation does proceed in the absence of ligand **2**[15] (Table 1, entry 3). Pybox ligands other than **2** furnish lower *ee* values and yields (Table 1, entries 4 and 5), as do solvents other than a glyme/THF mixture (Table 1, entries 6–8). At room temperature, the catalyst system is somewhat less effective than at −30 °C (Table 1, entry 9).

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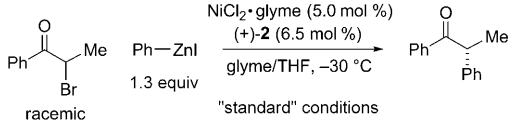
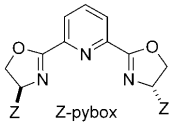
Table 1: Catalytic asymmetric arylations of racemic α-bromoketones: Effect of reaction parameters.



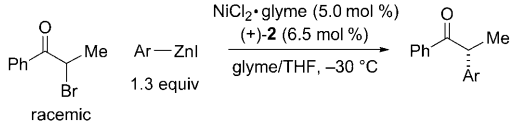
Entry	Variation from the "standard" conditions	*ee* [%]	Yield [%][a]
1	none	94	87
2	no $NiCl_2$·glyme	–	< 5
3	no (+)-**2**	–	55
4	Ph-pybox, instead of (+)-**2**	71	54
5	*i*Pr-pybox, instead of (+)-**2**	73	6
6	glyme only	–	< 5
7	THF only	87	52
8	DMF, instead of glyme/THF	–	< 5
9	RT	89	81

[a] The yield was determined by using GC methods with a calibrated internal standard.



By using our optimized method, we can achieve Negishi cross-couplings of racemic 2-bromopropiophenone with an array of arylzinc reagents with excellent *ee* values and good yields (Table 2),[16] although the efficiency of the process is

Table 2: Catalytic asymmetric arylations of racemic α-bromoketones: Variation of the nucleophile.



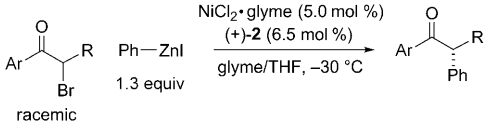
Entry	Ar	*ee* [%]	Yield [%][a]
1	Ph	96 (95[b])	86 (88[b])
2	2-MeO-C_6H_4	–	< 5
3	3-Me-C_6H_4	94	88
4[b]	3-MeO-C_6H_4	94	87
5	4-F-C_6H_4	96	74
6	4-MeO-C_6H_4	96	93
7	4-Me_2N-C_6H_4	93	85
8	4-MeS-C_6H_4	96	71

All data are the average of two experiments. [a] Yield of purified product. [b] Ar_2Zn (1.1 equiv) was used, rather than ArZnI.

sensitive to the steric demand of the nucleophile (Table 2, entry 2). The organozinc substrate can include a range of functional groups, such as OR, halogen, NR_2, and SR groups. Diarylzinc reagents (Ar_2Zn) and arylzinc iodides (ArZnI) generally furnish similar enantioselectivities and yields (e.g., Table 2, entry 1).[17] The α-arylated ketone is stable to racemization under these conditions.

We have examined the scope of this method for the catalytic asymmetric α-arylation of ketones not only with respect to the nucleophile (Table 2), but also the electrophile (Table 3). Very good *ee* values and useful yields are observed with a variety of α-alkyl substituents, including those that are functionalized (Table 3, entries 2 and 3) and β branched

Table 3: Catalytic asymmetric arylations of racemic α-bromoketones: Variation of the electrophile.



Entry	Ar	R	*ee* [%]	Yield [%][a]
1	Ph	Et	94	86
2	Ph	CH_2Ph	95	76
3[b]	Ph	CH_2CH_2Cl	92	90
4[c]	Ph	*i*Bu	95	89
5	Ph	*i*Pr	–	< 5
6	2-F-C_6H_4	Me	72	80
7[b]	2-Et-C_6H_4	Me	75	79
8	4-MeO-C_6H_4	Me	96	90
9	4-F_3C-C_6H_4	Me	87 (89)[c]	76 (82)[c]
10	2-thienyl	Me	96	81

All data are the average of two experiments. [a] Yield of purified product. [b] Run at −20 °C. [c] Ar_2Zn (1.1 equiv) was used rather than ArZnI.

(Table 3, entry 4); however, if R is large, little of the cross-coupling product is formed (Table 3, entry 5). If the aryl group of the ketone is bulky, the reaction proceeds with moderate enantioselectivity (Table 3, entries 6 and 7). In contrast, good *ee* values are observed regardless of whether the group is electron-rich (Table 3, entry 8) or electron-poor (Table 3, entry 9). A thiophene is compatible with this nickel-based coupling process (Table 3, entry 10).[18]

In conclusion, we have developed the first catalytic asymmetric method for cross-coupling arylmetal reagents with α-haloketones, specifically, the $NiCl_2$·glyme/**2**-catalyzed reaction of arylzincs with racemic secondary α-bromoketones. This stereoconvergent carbon–carbon bond-forming process occurs under unusually mild conditions (−30 °C and no activators), thereby allowing the generation of potentially labile tertiary stereocenters. Ongoing efforts are directed at expanding the scope of cross-coupling reactions of alkyl electrophiles.

Experimental Section

General Procedure: A solution of the arylmagnesium bromide (1.6 mmol; 1.6 equiv) was added to a solution of ZnI_2 (510 mg, 1.6 mmol; 1.6 equiv) in THF (final concentration of ArZnI = 0.20 M) under argon. The mixture was stirred for 40 min at room temperature (a precipitate is immediately observed), and then it was cooled to −30 °C. $NiCl_2$·glyme (11.0 mg, 0.050 mmol; 0.050 equiv) and (+)-**2** (29.9 mg, 0.065 mmol; 0.065 equiv) were added to an oven-dried 50 mL flask. The flask was purged with argon, and then the α-bromoketone (1.0 mmol; 1.0 equiv) and glyme (13.5 mL) were added in that order. This solution was stirred at room temperature for 20 min, and then it was cooled to −30 °C. The suspension of ArZnI (6.5 mL, 1.3 mmol; 1.3 equiv) was added dropwise over 3 min, and the reaction mixture was stirred at −30 °C for 4 h. The reaction was then

quenched with saturated ammonium chloride (10 mL). The reaction mixture was diluted with Et_2O (50 mL) and distilled water (10 mL). The organic layer was separated, washed with brine (10 mL), dried over magnesium sulfate, and concentrated. The product was purified by flash column chromatography.

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[1] For some leading references, see: J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360 – 1370.
[2] For overviews, see: a) Reference [1]; b) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 – 245.
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[9] We believe that, in certain cases, even the product of the Hiyama arylation illustrated in Equation (1) may be susceptible to racemization (e.g., with Ar = 4-F_3C-C_6H_4; see footnote 7a of reference [8]).
[10] For asymmetric Negishi alkylations of α-haloamides, see: C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594 – 4595.
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[15] Ligand **2** can be synthesized in one or two steps from a commercially available amino alcohol and a commercially available pyridine derivative (see the Supporting Information).
[16] Notes: a) In preliminary studies under our standard conditions, α-chloroketones and heteroarylzinc reagents were not suitable substrates (low yield or *ee* values); b) During the course of the cross-coupling, the *ee* value of the unreacted α-bromoketone was less than 5%, and the *ee* value of the product was essentially constant.
[17] Notes: a) The use of less than 1.1 equivalent of Ar_2Zn (2.2 equiv of the Ar group) leads to significantly lower yields. Therefore, we generally employ ArZnI (1.3 equiv) as the arylating agent; b) We prepared ArZnI by the reaction of a Grignard reagent with ZnI_2. In preliminary experiments, we observed that arylzinc halides produced by zinc insertion into aryl halides may also be employed, whereas the use of commercially available arylzinc halides led to lower yields.
[18] In a preliminary study, we obtained 72% *ee* and 68% yield in a Negishi phenylation of racemic 2-bromocyclohexanone. To the best of our knowledge, there has been no previous report of a catalytic asymmetric arylation of a dialkylketone (see references [3] and [4]).

