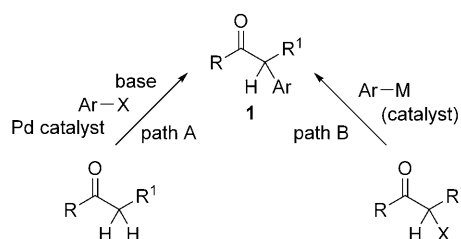


Catalytic Asymmetric Cross-Couplings of Racemic α -Bromoketones with Arylzinc Reagents**

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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]

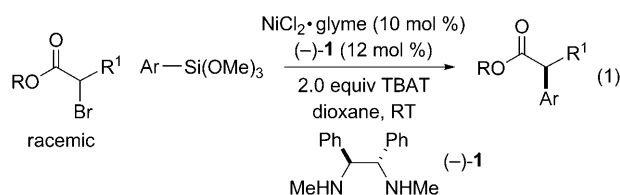


Scheme 1. Methods for synthesizing ketones having α -aryl substituents.

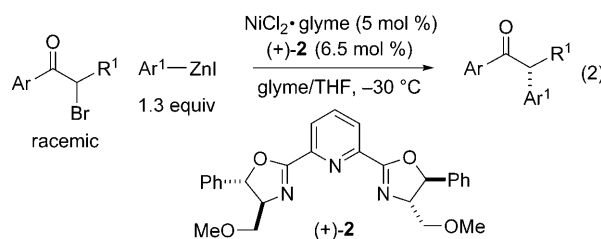
Furthermore, in the case of α,α -disubstituted ketones, catalytic asymmetric α -arylations have been described wherein quaternary stereocenters are generated with excellent enantioselectivity.^[3,4] Unfortunately, these methods cannot be applied to the asymmetric synthesis of more commonly encountered 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 = $[\text{F}_2\text{SiPh}_3]^- [\text{NBu}_4]^+$].^[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 $\text{NiCl}_2\cdot\text{glyme}$ 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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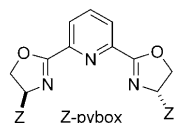
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Table 1: Catalytic asymmetric arylations of racemic α -bromoketones: Effect of reaction parameters.

"standard" conditions			
Entry	Variation from the "standard" conditions	<i>ee</i> [%]	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>i</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.

racemic			
Entry	Ar	<i>ee</i> [%]	Yield [%] ^[a]
1	Ph	96 (95 ^[b])	86 (88 ^[b])
2	2-MeO-C ₆ H ₄	—	< 5
3	3-Me-C ₆ H ₄	94	88
4 ^[b]	3-MeO-C ₆ H ₄	94	87
5	4-F-C ₆ H ₄	96	74
6	4-MeO-C ₆ H ₄	96	93
7	4-Me ₂ N-C ₆ H ₄	93	85
8	4-MeS-C ₆ H ₄	96	71

All data are the average of two experiments. [a] Yield of purified product. [b] Ar₂Zn (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, NR₂, and SR groups. Diarylzinc reagents (Ar₂Zn) 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.

racemic				
Entry	Ar	R	<i>ee</i> [%]	Yield [%] ^[a]
1	Ph	Et	94	86
2	Ph	CH ₂ Ph	95	76
3 ^[b]	Ph	CH ₂ CH ₂ Cl	92	90
4 ^[c]	Ph	<i>i</i> Bu	95	89
5	Ph	<i>i</i> Pr	—	< 5
6	2-F-C ₆ H ₄	Me	72	80
7 ^[b]	2-Et-C ₆ H ₄	Me	75	79
8	4-MeO-C ₆ H ₄	Me	96	90
9	4-F ₃ C-C ₆ H 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] Ar₂Zn (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 NiCl₂·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 ZnI₂ (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 . NiCl₂·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 Et₂O (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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- [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 Ar₂Zn (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 ZnI₂. 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]).