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Nickel/Bis(oxazoline)-Catalyzed Asymmetric Kumada Reactions of Alkyl Electrophiles: Cross-Couplings of Racemic α-Bromoketones

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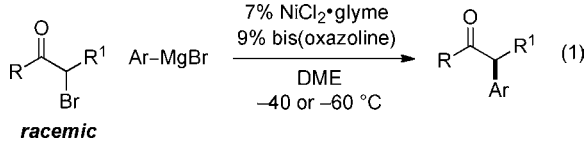
Transition-metal-catalyzed couplings of organic electrophiles with Grignard reagents ("Kumada reactions") were among the first cross-coupling processes that were discovered.[1,2] Like other families of cross-couplings, this versatile method for the synthesis of carbon−carbon bonds has been applied primarily to reactions of aryl and vinyl electrophiles.[3] It is nevertheless noteworthy that the earliest successes in cross-coupling *alkyl* electrophiles were Kumada-type reactions with Grignard reagents.[4−6] Despite that initial progress, to date there have been no examples of *enantioselective* Kumada couplings of *alkyl* electrophiles.[7−9] In this report, we begin to address this challenge, establishing that a Ni/bis(oxazoline) catalyst achieves asymmetric cross-couplings of α-bromoketones with aryl Grignard reagents (eq 1).[10,11]



With respect to enantioselective cross-coupling reactions of alkyl electrophiles, pybox ligands have proved to be useful for an array of nickel-catalyzed Negishi reactions, whereas 1,2-diamine ligands have found application in Hiyama and Suzuki reactions.[8] Unfortunately, none of the previously described methods achieves the asymmetric Kumada coupling illustrated in entry 1 of Table 1 in good ee and yield.

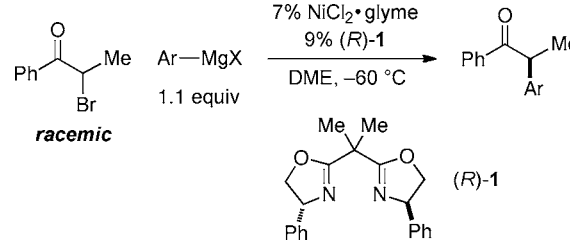
Although bis(oxazoline) ligands have been widely applied in metal-catalyzed processes,[12] to the best of our knowledge they have not been employed in cross-coupling reactions of alkyl electrophiles. We have determined that, in the presence of an appropriate C_2-symmetric bis(oxazoline), the desired Kumada coupling proceeds both in good yield and with high enantioselectivity (entry 1 of Table 1; $NiCl_2$·glyme and ligand **1** are commercially available).

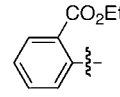
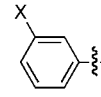
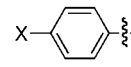
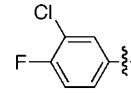
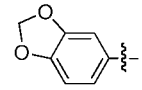
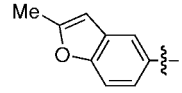
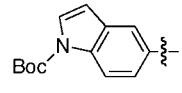
Several features of this asymmetric Kumada reaction are noteworthy. First, the cross-coupling is stereoconvergent: both enantiomers of the electrophile are converted efficiently into the same enantiomer of the product.[8] Second, the reaction occurs at −60 °C, the lowest temperature that has been employed to date for a cross-coupling of an alkyl electrophile (activated or unactivated).[13] Third, as a consequence of the low temperature, the potentially labile α-arylketone product is not racemized under the Brønsted-basic conditions.[14]

Exploiting a procedure developed by Knochel for the synthesis of functionalized Grignard reagents,[15] we have demonstrated that a wide array of aryl Grignards can be employed in our enantioselective Kumada cross-couplings (Table 1).[16,17] The method is compatible with a diverse spectrum of functional groups, including esters, halides (no aryl−aryl coupling), nitriles, ethers, and heteroaromatic rings (e.g., benzofurans and indoles).[18] Regardless of the electron-withdrawing or electron-donating nature of the substituent on the aromatic ring, consistently good ee's and yields are obtained.

A variety of α-bromoketones are suitable electrophilic partners in this catalytic asymmetric Kumada cross-coupling process. In

Table 1. Asymmetric Kumada Reactions of α-Bromoketones: Variation of the Nucleophile[a]

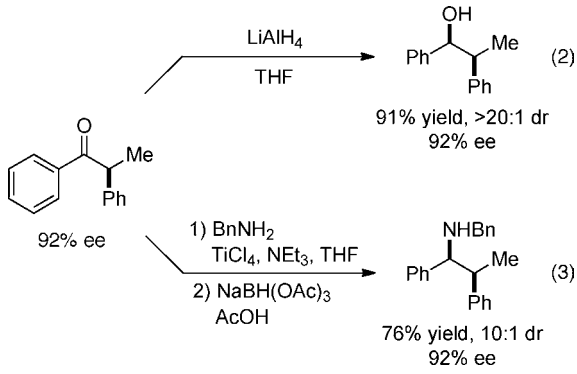


entry	Ar		ee (%)	yield (%)[b]
1	Ph		92	81
2			80	79
3		X = Br	93	76
4		CN	95	91
5		OMe	92	76
6		X = CF_3	94	84
7		CO_2Et	95	91
8		I	94	83
9		OMe	91	82
10			95	76
11			92	75
12			91	87
13			90	73

[a] All data are the average of two experiments. [b] Yield of purified product.

10.1021/ja909689t

the case of aryl alkyl ketones (Table 2), the aromatic group can be electron-rich or electron-poor, and it can bear a variety of substitution patterns (entries 1−6). Furthermore, the coupling proceeds smoothly with a heteroaromatic substituent (entry 7), as well as with an array of functionalized alkyl groups (entries 9−11). The cross-coupling products can be derivatized with good diastereoselectivity without racemization (eqs 2 and 3).[19]

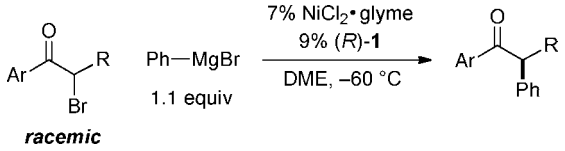


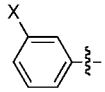
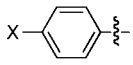
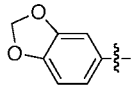
When the same conditions are applied to asymmetric Kumada reactions of dialkyl ketones, more modest enantioselectivities are observed (for entry 1 of Table 3, 23% ee and 24% yield). However, by modifying the structure of the bis(oxazoline) and raising the reaction temperature, we have obtained promising ee's for a variety of reaction partners (Table 3). To the best of our knowledge, with a single exception,[20] there had been no previous progress in such catalytic asymmetric cross-couplings of dialkyl ketones.

Some preliminary observations may be useful in contemplating the mechanism for this process. A kinetic study of the cross-coupling of 2-bromo-1-phenylpropan-1-one with PhMgBr (entry 1 of Table 1) revealed that the rate law for the reaction is first order in nickel, first order in PhMgBr, and zero order in the electrophile.[21] In addition, the unreacted electrophile is essentially racemic throughout the course of the reaction (<5% ee; no evidence for kinetic resolution). Finally, the ee of the product correlates linearly with the ee of the ligand (no nonlinear effect).

In summary, we have described the first asymmetric Kumada reactions of alkyl electrophiles, specifically, couplings of racemic α-bromoketones with aryl Grignard reagents. This adds to the small but growing list of cross-couplings of alkyl electrophiles that can be achieved with useful enantioselectivity. Several features of this investigation are noteworthy. First, the couplings proceed at remarkably low temperature (−40 or −60 °C), which enables the asymmetric synthesis of racemization-prone α-arylketones. Second, *dialkyl* ketones undergo enantioselective coupling

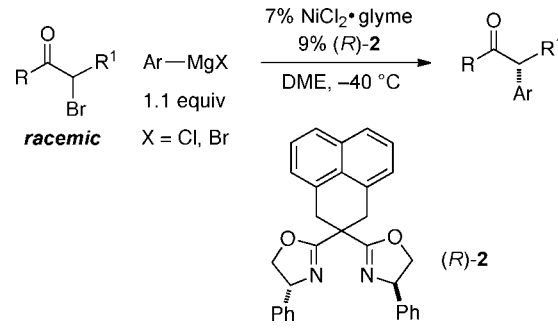
Table 2. Asymmetric Kumada Reactions of Aryl Alkyl Ketones[a]

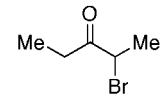
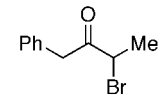
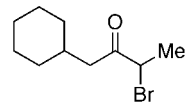
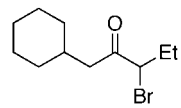
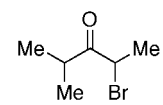
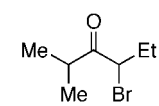


entry	Ar		R	ee (%)	yield (%)[b]
1			Me	72	89
2		X = Cl	Me	80	72
3		OMe	Me	92	81
4		X = Br	Me	80	80
5		OBn	Me	90	80
6			Me	90	76
7			Me	87	91
8	Ph		Et	90	77
9	Ph			86	73
10	Ph			80	72
11	Ph			85	74

[a] All data are the average of two experiments. [b] Yield of purified product.

Table 3. Asymmetric Kumada Reactions of Dialkyl Ketones[a]



entry	ketone	Ar	ee (%)	yield (%)[b]
1		Ph	73	90
2		Ph	85	74
3		4-Cl-C_6H_4	90	82
4		4-CO_2Et-C_6H_4	81	79
5		4-OMe-C_6H_4	90	73
6		Ph	85	73
7		3-Br-C_6H_4	78	70
8		Ph	84	83
9		3,4-OCH_2O-C_6H_3	83	75
10		4-CO_2Et-C_6H_4	80	78

[a] All data are the average of two experiments. [b] Yield of purified product.

in good ee and yield. Third, readily available bis(oxazolines) have been shown for the first time to be effective ligands for cross-couplings of alkyl electrophiles, thereby opening the door to exciting new opportunities in asymmetric catalysis.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For examples of catalytic enantioselective cross-coupling reactions of activated and unactivated alkyl electrophiles with other families of nucleophiles, see: (a) Negishi alkylation of α-bromoamides: Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (b) Negishi alkylation of benzylic halides: Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Negishi alkylation of allylic chlorides: Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757. (d) Hiyama arylation and vinylation of α-bromoesters: Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303. (e) Alkynylation of benzylic bromides: Caeiro, J.; Sestelo, J. P.; Sarandeses, L. A. *Chem.−Eur. J.* **2008**, *14*, 741–746. (f) Suzuki alkylation of homobenzylic bromides: Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (g) Negishi arylation of propargylic halides: Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647. (h) Negishi arylation of α-bromoketones: Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed* **2009**, *48*, 154–156.
(9) For an overview of asymmetric cross-couplings of secondary alkyl halides, see: Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347–8349.
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(12) For examples and leading references, see: Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505–2550.
(13) To the best of our knowledge, the lowest temperature previously employed for a cross-coupling of an alkyl electrophile was −30 °C (ref 8h).
(14) Although no racemization of the product occurs after 24 h at −60 °C, significant racemization is observed at room temperature.
(15) (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701–1703. (b) For a review, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.
(16) (a) For the cross-coupling illustrated in entry 1 of Table 1: on a gram scale (5% $NiCl_2$·glyme/6.5% bis(oxazoline)), the reaction proceeds in 92% ee and 80% yield; no carbon−carbon bond formation is observed in the absence of $NiCl_2$·glyme ($NiBr_2$·glyme or $Ni(cod)_2$ may be used in place of $NiCl_2$·glyme); in the absence of the bis(oxazoline) ligand, the product is generated in 22% yield; the ee of the product is constant during the cross-coupling; in a competition experiment, an unactivated alkyl bromide is recovered in essentially quantitative yield; and use of a solution of the Grignard reagent in THF results in a somewhat lower ee and yield. (b) The efficiency of this method is sensitive to the steric demand of the coupling partners. (c) α-Chloroketones are not suitable substrates under these conditions.
(17) *Sample experimental procedure:* A 20-mL vial equipped with a stir bar was capped with a septum and taped. The vial was purged with argon for 2 min, and then 1,2-dimethoxyethane (8 mL) was added by syringe, followed by the aryl iodide (1.10 mmol). The solution was cooled to −20 °C, and a solution of *i*-PrMgCl (2.0 M solution in Et_2O; 0.55 mL, 1.1 mmol) was added over 1 min. The resulting mixture was stirred at −20 °C for 1−2 h, and then it was cooled to −60 °C. Ligand (*R*)-**1** (30.0 mg, 0.090 mmol) and $NiCl_2$·glyme (15.3 mg, 0.070 mmol) were added to a 4-mL vial equipped with a stir bar. The vial was capped with a septum, taped, and gently purged with argon for 1 min. 1,2-Dimethoxyethane (2.0 mL) was added, and this solution of the catalyst was stirred at room temperature for 5 min. Next, the α-bromoketone (1.0 mmol) was added, and the mixture was stirred at room temperature for 5 min. Then, the resulting homogeneous dark-pink solution was added dropwise over 3 min to the −60 °C solution of the Grignard reagent. The resulting yellow solution was stirred at −60 °C for 16−32 h. Next, the reaction was quenched with ethanol (2 mL), and the resulting mixture was filtered through a Büchner funnel that contained a bed of silica gel. The silica gel was washed with Et_2O (40 mL), and the combined filtrates were concentrated by rotary evaporation. The resulting residue was purified by flash chromatography.
(18) Under our standard conditions, our initial attempts to couple heteroaromatic Grignard reagents such as 2-pyridylmagnesium chloride and 3-thienylmagnesium chloride were not successful.
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