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

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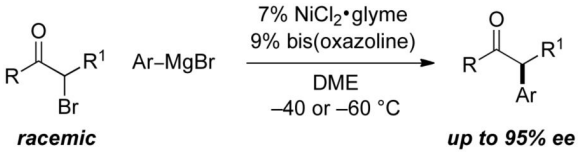
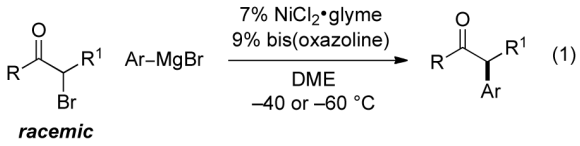
Abstract



The first asymmetric Kumada reactions of alkyl electrophiles are described, specifically, cross-couplings of racemic α-bromoketones with aryl Grignard reagents. Several features of this investigation are of interest. First, the couplings proceed at remarkably low temperature (−40 °C or −60 °C), which enables the asymmetric synthesis of racemization-prone α-arylketones. Second, *dialkyl* ketones undergo enantioselective coupling in good ee and yield. Third, readily available bis (oxazolines) are shown for the first time to be effective ligands for cross-couplings of alkyl electrophiles, thereby opening the door to new opportunities in asymmetric catalysis.

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.[4,5,6] Despite that initial progress, to date there have been no examples of *enantioselective* Kumada couplings of *alkyl* electrophiles.[7,8,9] 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

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of the previously described methods achieves the asymmetric Kumada coupling illustrated in entry 1 of Table 1 in good ee and yield.

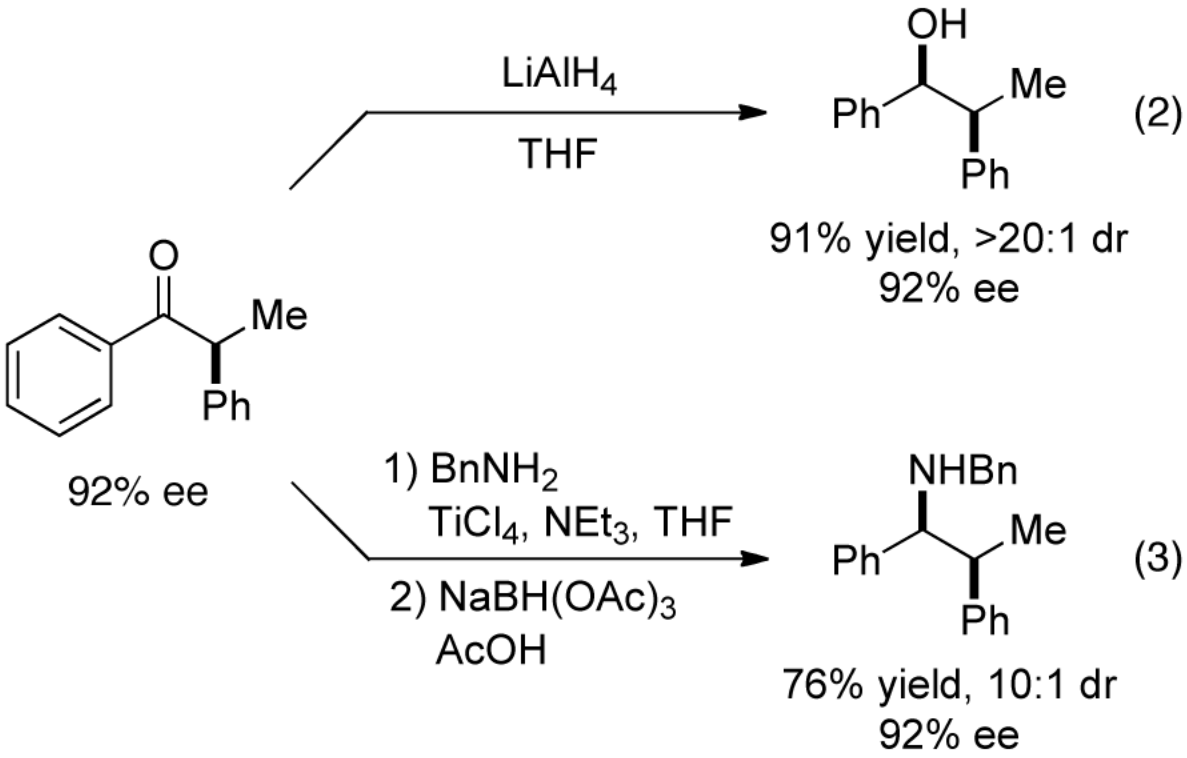
Although bis(oxazoline) ligands have been widely applied in metal-catalyzed processes,[12] to the best of our knowledge they have not been employed in cross-coupling reactions of alkyl electrophiles. We have determined that, in the presence of an appropriate C_2-symmetric bis (oxazoline), the desired 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 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 (eq 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 non-linear 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 °C or −60 °C), which enables the asymmetric synthesis of racemization-prone α-arylketones. Second, *dialkyl* ketones undergo enantioselective coupling 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

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(2). For pioneering studies of nickel-catalyzed processes, see:(a) Tamao K, Sumitani K, Kumada M. J. Am. Chem. Soc 1972;94:4374–4376. (b) Corriu RJP, Masse JP. Chem. Commun 1972:144.

(3). For overviews of cross-coupling chemistry, see:(a) de Meijere, A.; Diederich, F., editors. Metal-Catalyzed Cross-Coupling Reactions. Wiley–VCH; New York: 2004. (b) Miyaura, N., editor. Topics in Current Chemistry. Vol. 219. Springer–Verlag; New York: 2002.

(4). For example, see:Tamura M, Kochi J. Synthesis 1971:303–305.

(5). For some recent work on nickel-catalyzed Kumada reactions of alkyl electrophiles (including leading references), see:(a) Terao J, Kambe N. Acc. Chem. Res 2008;41:1545–1554. [PubMed: 18973349] (b) Vechorkin O, Proust V, Hu X. J. Am. Chem. Soc 2009;131:9756–9766. [PubMed: 19552426]

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(10). For leading references to target molecules that include ketones that bear an α-aryl group, see:Fox JM, Huang X, Chieffi A, Buchwald SL. J. Am. Chem. Soc 2000;122:1360–1370.

(11). The catalytic enantioselective synthesis of α-arylketones that bear *tertiary* stereocenters has not been achieved via the cross-coupling of ketone enolates with aryl electrophiles, due to racemization of the product under the Brønsted-basic reaction conditions. For key studies and discussions regarding the catalytic asymmetric synthesis of α-arylketones that bear *quaternary* stereocenters, see:(a) Åhman J, Wolfe JP, Troutman MV, Palucki M, Buchwald SL. J. Am. Chem. Soc 1998;120:1918–1919.Hamada T, Chieffi A, Åhman J, Buchwald SL. J. Am. Chem. Soc 2002;124:1261–1268. [PubMed: 11841295] (b) Liao X, Weng Z, Hartwig JF. J. Am. Chem. Soc 2008;130:195–200. [PubMed: 18076166] (c) Chen G, Kwong FY, Chan HO, Yu W-Y, Chan ASC. Chem. Commun 2006:1413–1415.

(12). For examples and leading references, see:Hargaden GC, Guiry PJ. Chem. Rev 2009;109:2505–2550. [PubMed: 19378971]

(13). To the best of our knowledge, the lowest temperature previously employed for a cross-coupling of an alkyl electrophile was −30 °C (Reference 8h).

(14). Although no racemization of the product occurs after 24 hours 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.For a review, see: (b) Knochel P, Dohle W, Gommermann N, Kneisel FF, Kopp F, Korn T, Sapountzis I, Vu VA. Angew. Chem., Int. Ed 2003;42:4302–4320.

(16). Notes: (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 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.

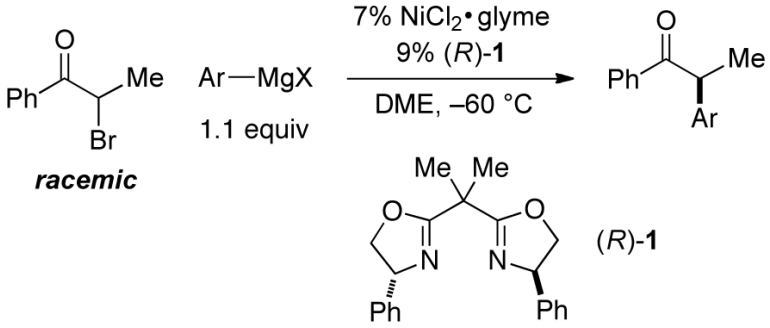
(19). For previous examples, see:(a) Cram DJ, Elhafez FAA. J. Am. Chem. Soc 1952;74:5828–5835. (b) Vicario JL, Badia D, Dominguez E, Carrillo L. J. Org. Chem 1999;64:4610–4616. [PubMed: 11674530]

(20). See footnote 18 in Reference [8h].

(21). This rate law can be accommodated by a reaction pathway proposed by Vicic:(a) Jones GD, Martin JL, McFarland C, Allen OR, Hall RE, Haley AD, Brandon RJ, Konovalova T, Desrochers PJ, Pulay P, Vicic DA. J. Am. Chem. Soc 2006;128:13175–13183. [PubMed: 17017797] (b) Lin X, Phillips DL. J. Org. Chem 2008;73:3680–3688. [PubMed: 18410144]

Table 1

Asymmetric Kumada Reactions of α-Bromoketones: Variation of the Nucleophile



entry	Ar	ee (%)
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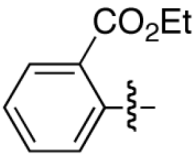
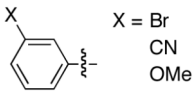
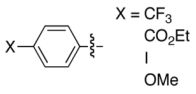
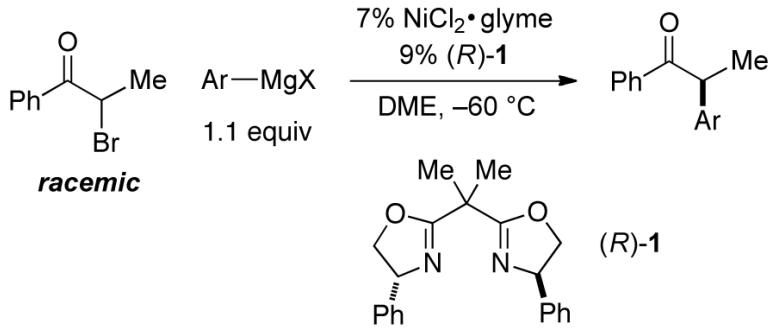
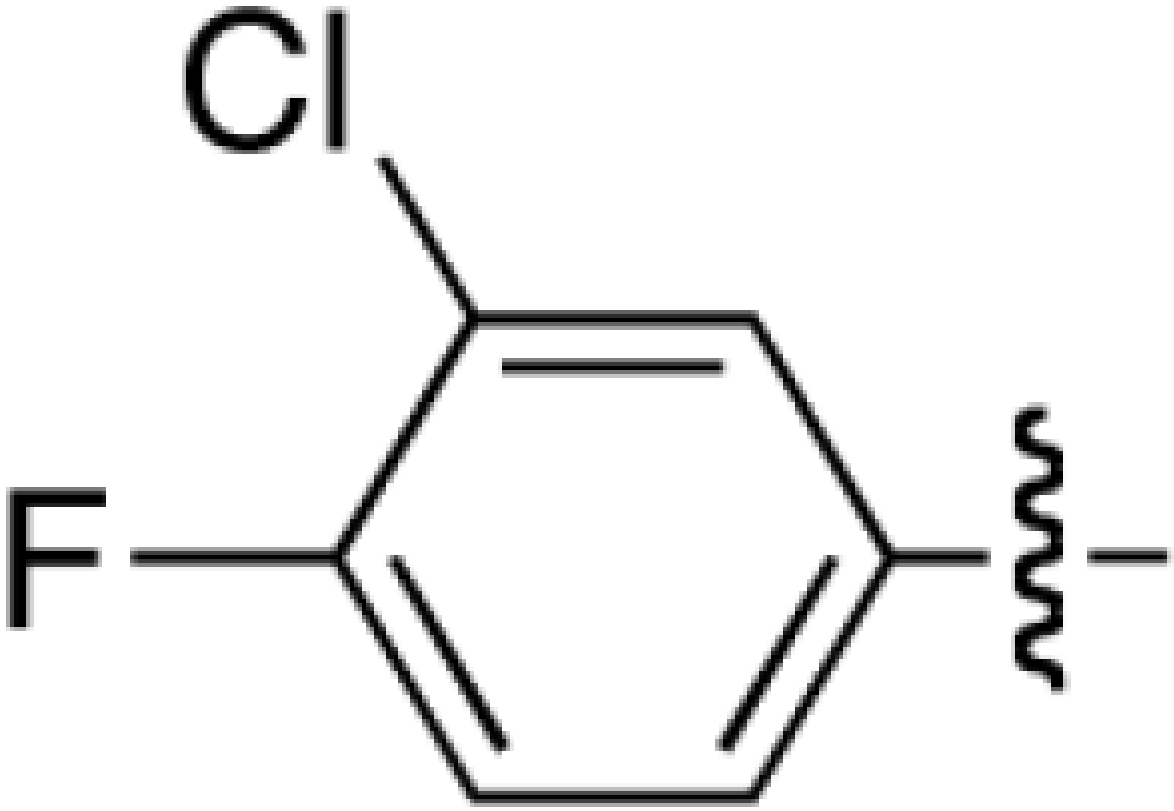
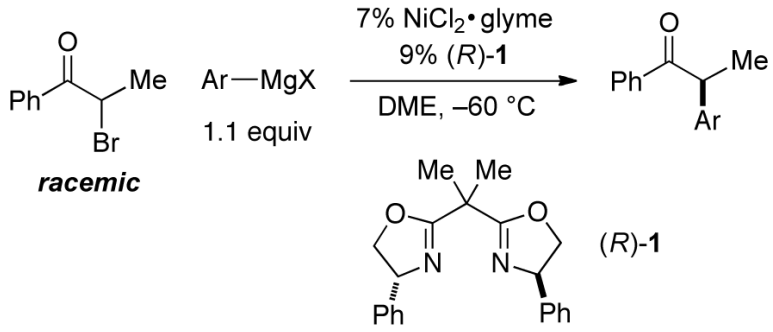
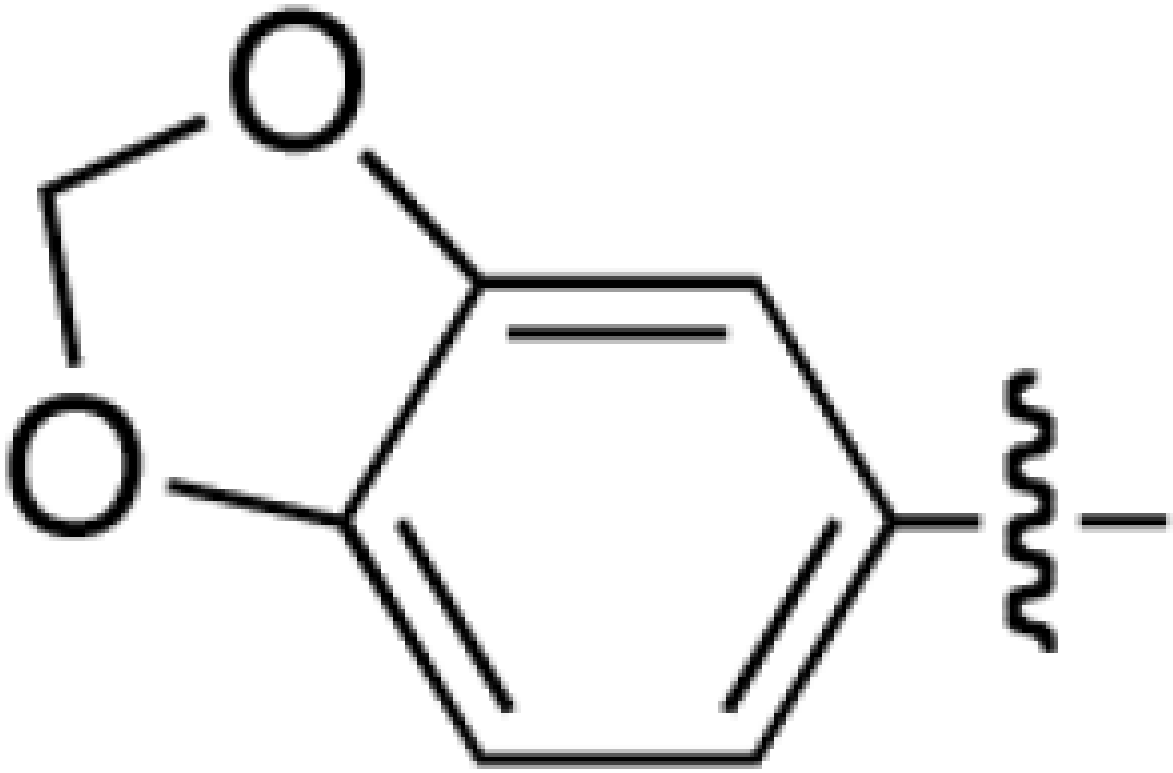
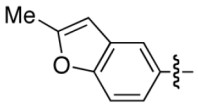
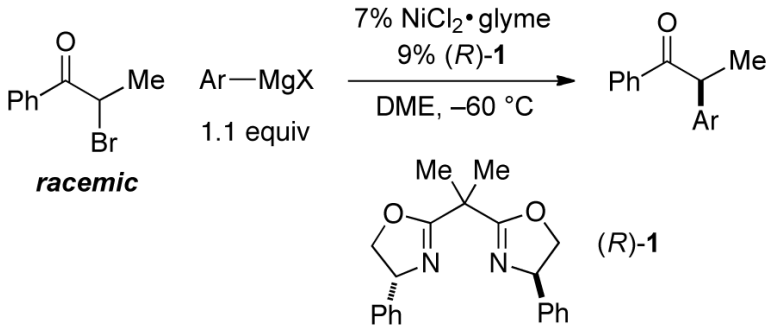
2		80
3	 X = Br	93
4	CN	95
5	OMe	92
6	 X = CF_3	94
7	CO_2Et	95
8	I	94
9	OMe	91



entry	Ar	ee (%)
10		95



entry	Ar	ee (%)
11		92
12		91



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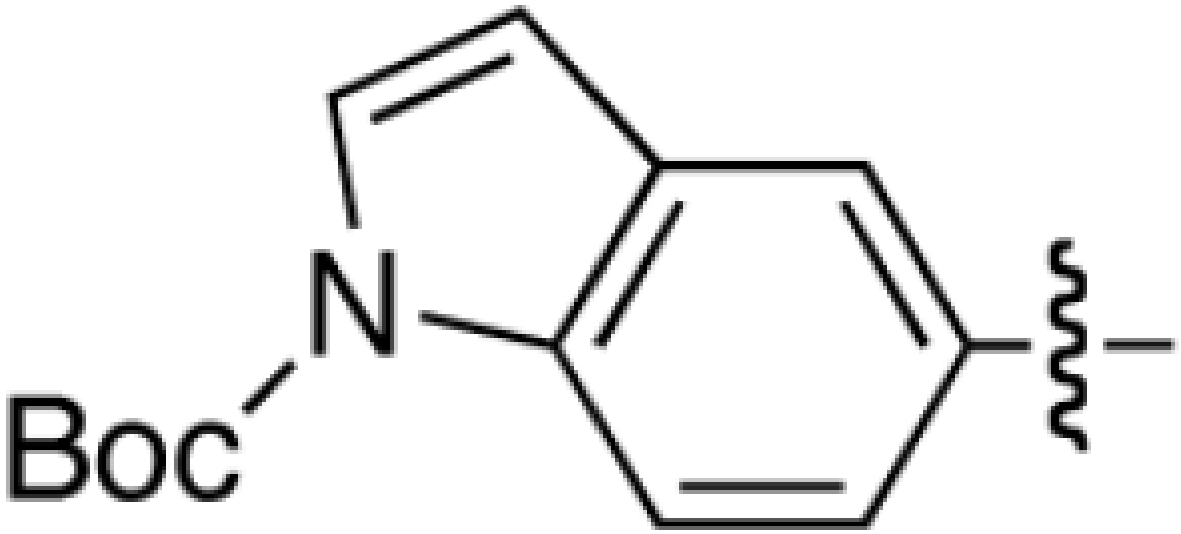
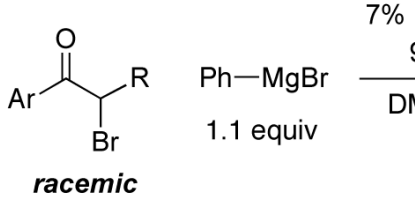
13		90

All data are the average of two experiments.

[a]Yield of purified product.

Table 2

Asymmetric Kumada Reactions of Aryl Alkyl Ketones



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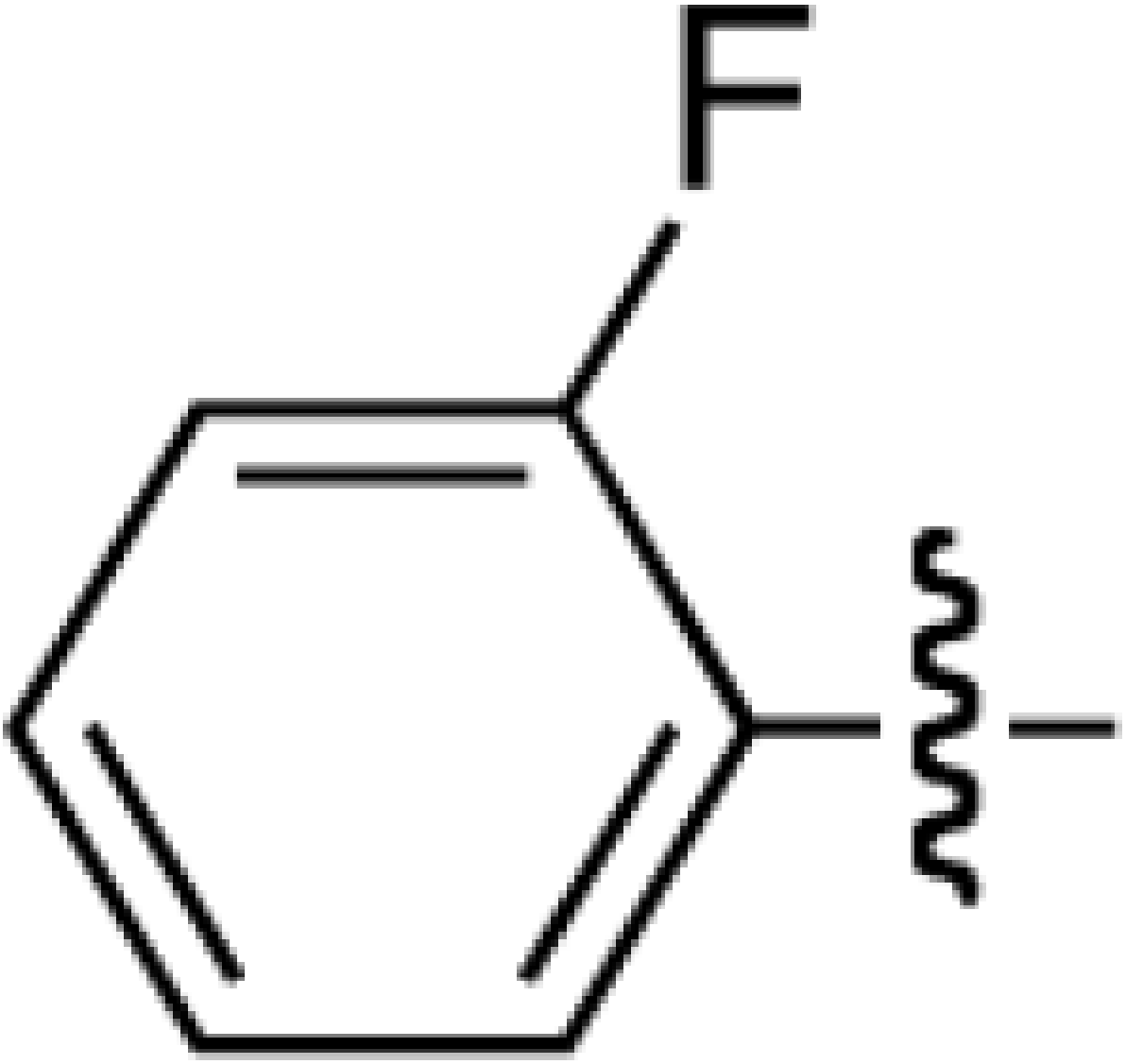
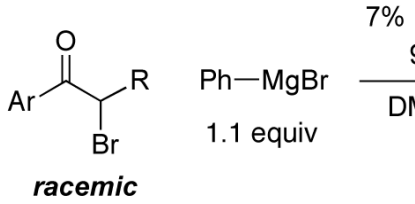
1	



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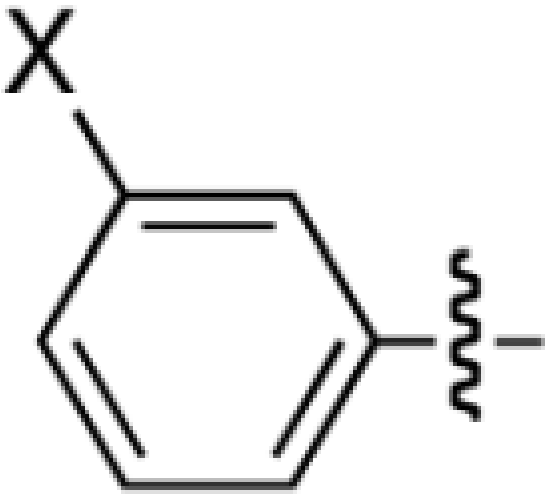
2	 
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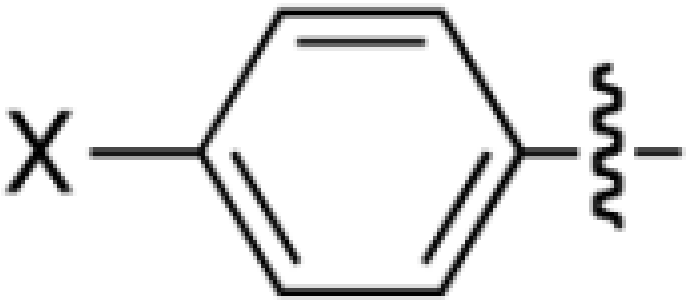
4	 
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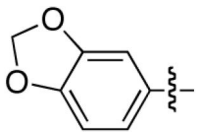
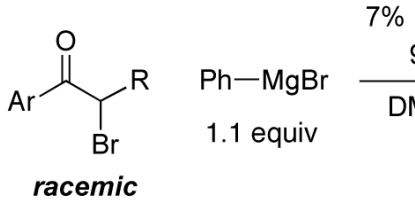
6	



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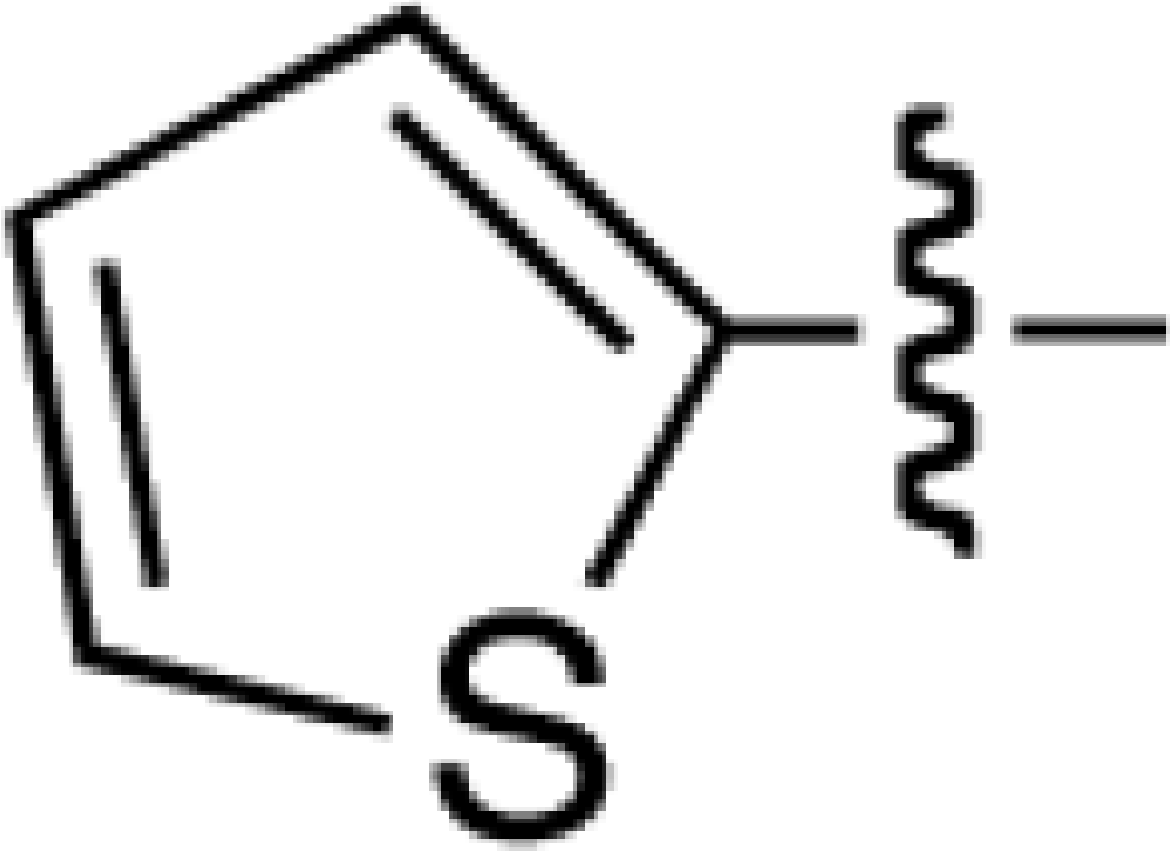
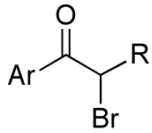
7	
8	Ph
9	Ph



racemic

Ph—MgBr
1.1 equiv

7%

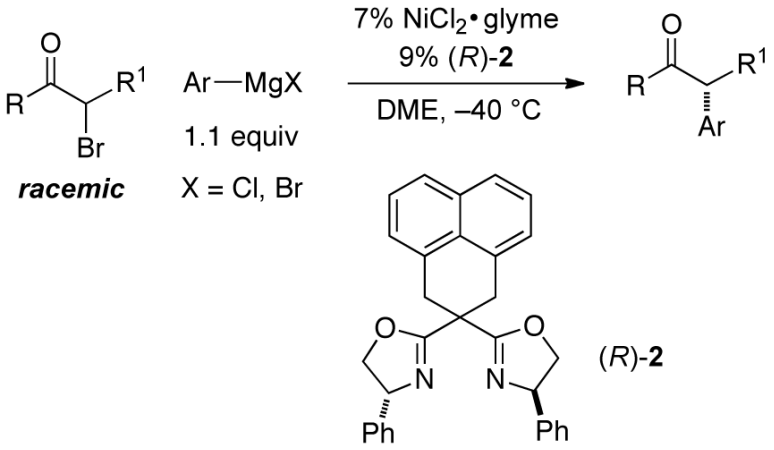
entry	Ar
10	Ph
11	Ph

All data are the average of two experiments.

[a] Yield of purified product.

Table 3

Asymmetric Kumada Reactions of Dialkyl Ketones



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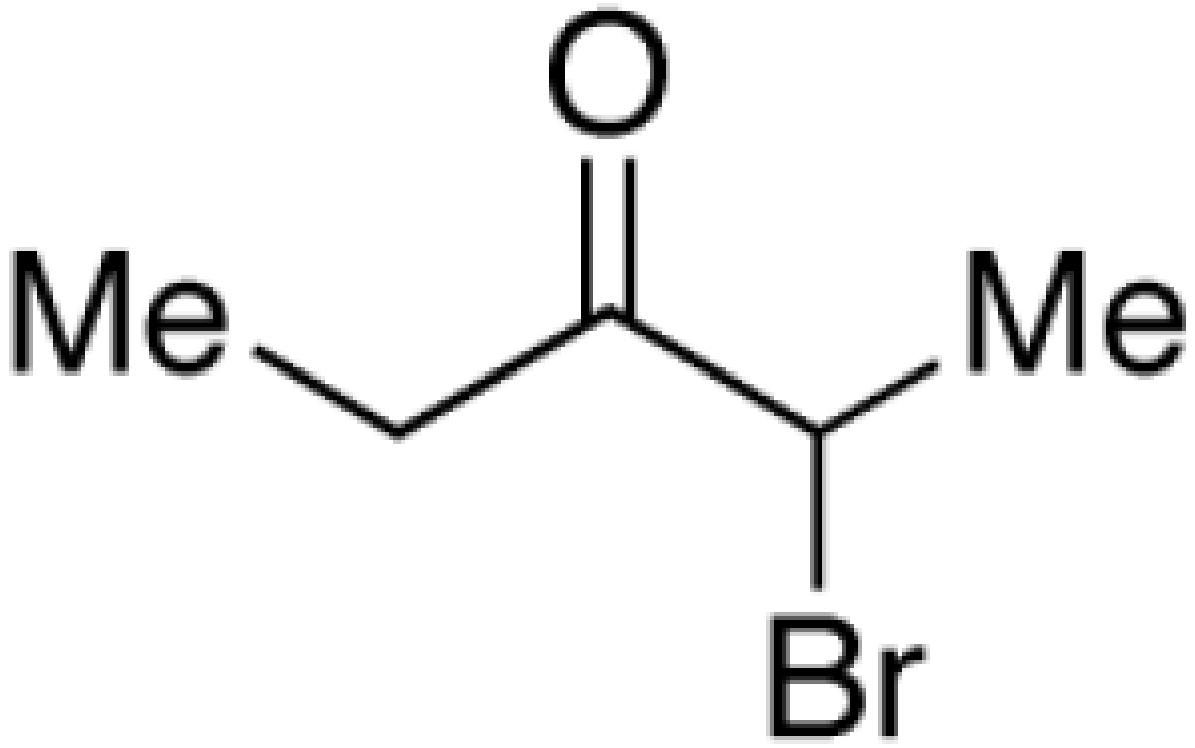
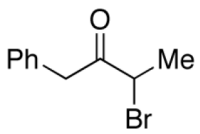
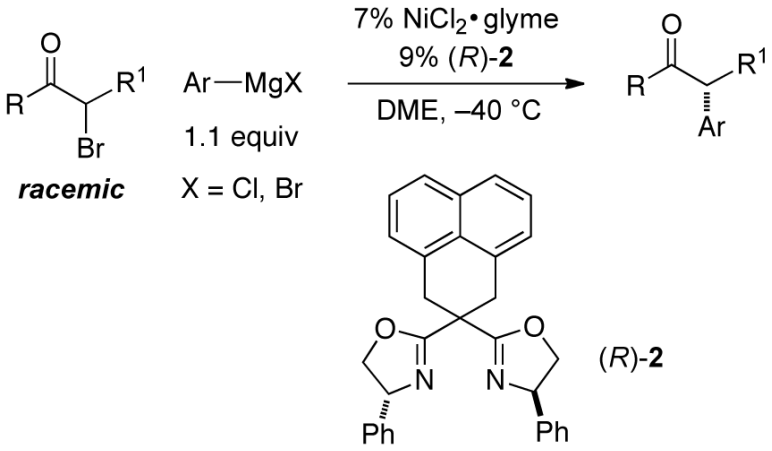
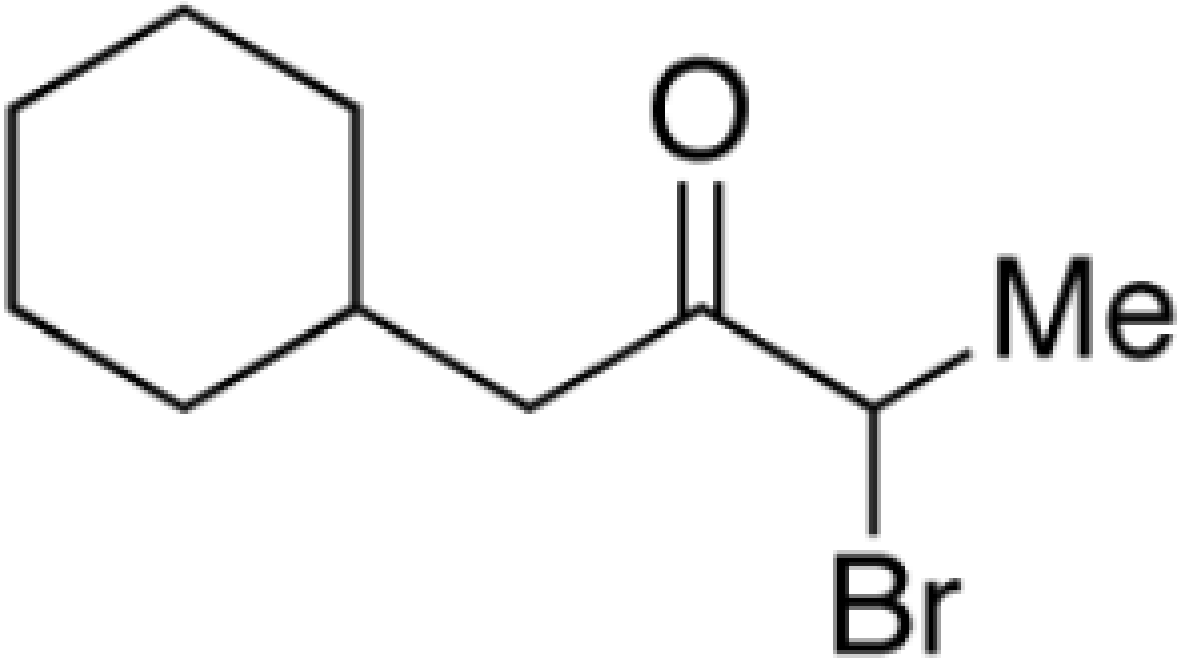
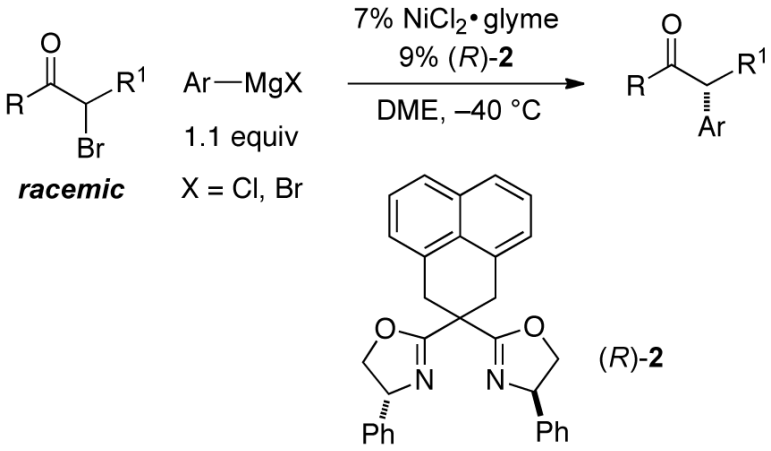
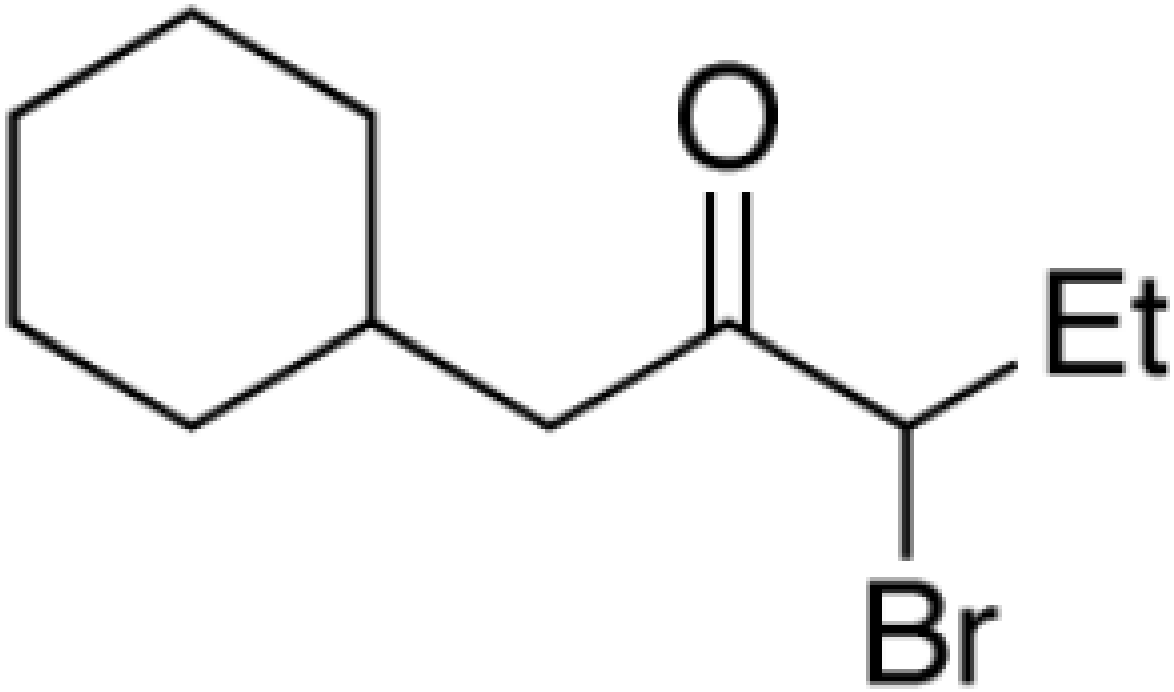
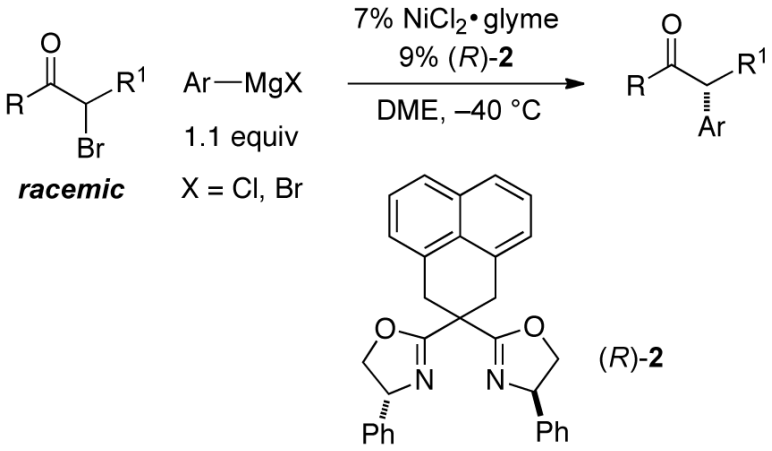
1		Ph
2		Ph
3		4-Cl-C_6H
4		4-CO_2Et-C
5		4-OMe-C

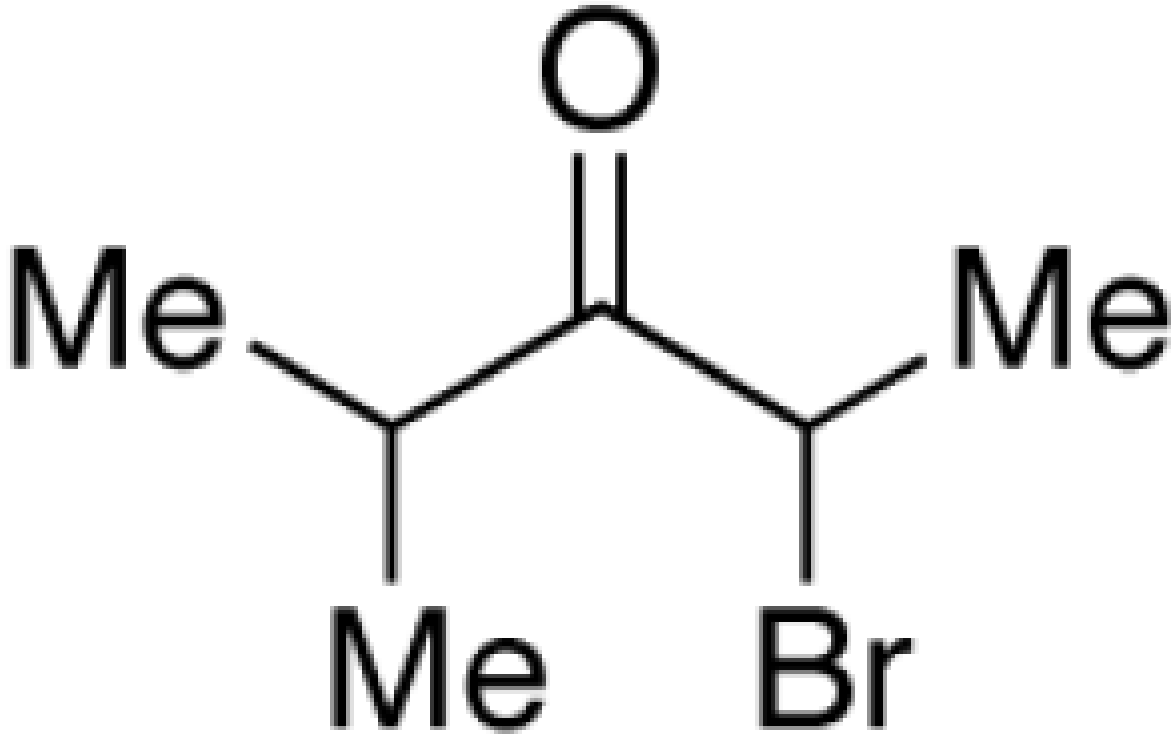


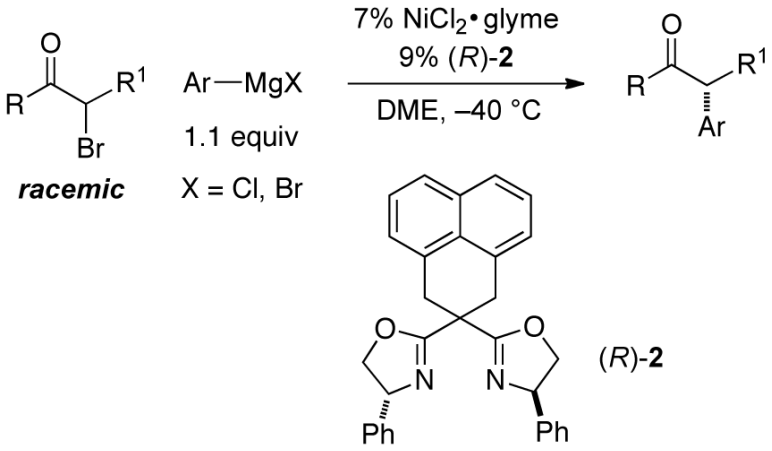
entry	ketone	Ar
6		Ph

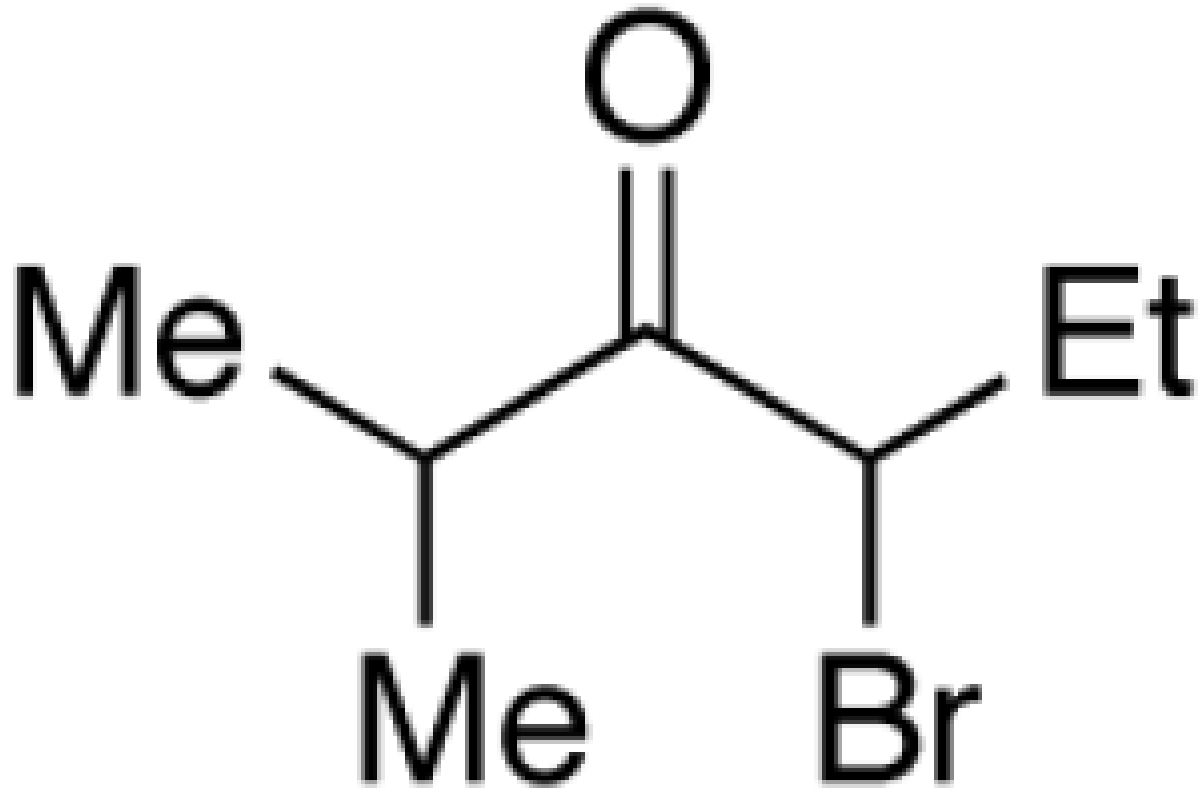


entry	ketone	Ar
7		3-Br-C_6H



entry	ketone	Ar
8		Ph
9		3,4-OCH_2



entry	ketone	Ar
10		4-CO_2Et-C

All data are the average of two experiments.

[a] Yield of purified product.