# Sodium-Ketyl Radical Anions by Reverse Pinacol Reaction and Their Coupling with Iodoarenes

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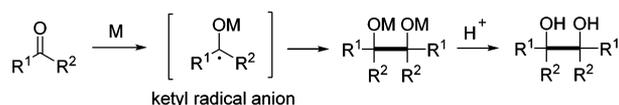
Ⓢ *Supporting Information*

ABSTRACT: Transition-metal-free C−C bond formation between aryl iodides and pinacols is presented. Pinacols are readily transformed by deprotonation with NaH to their Na-pinacolates. C−C-bond homolysis at room temperature generates in situ the corresponding Na-ketyl radical anions which react with various aryl iodides in a homolytic aromatic substitution reaction to form tertiary Na-alcoholates. Protonation eventually provides tertiary alcohols in an unprecedented route.
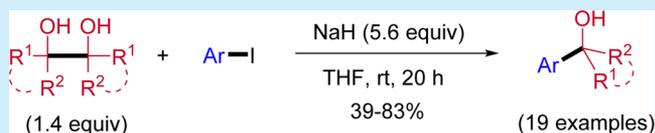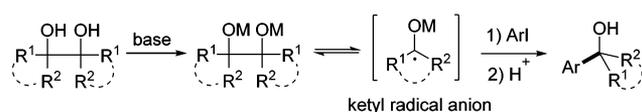
The pinacol coupling and follow up reactions such as the pinacol rearrangement have been amply used in organic synthesis.[1] Intermolecular pinacol homocoupling mostly occurs via reduction of a ketone precursor with a one-electron reducing reagent to give the corresponding ketyl radical anion which undergoes homocoupling to the pinacolate. Protonation eventually provides the pinacol coupling product (Scheme 1).[1]

Scheme 1. Pinacol and Reverse Pinacol Coupling in Synthesis

There are reports in the literature showing that the dimerization of a ketyl radical anion to the corresponding pinacolate can be reversible under certain conditions.[2] However, to our knowledge this reversibility has not been applied as a tool in synthetic organic chemistry to date. We assumed that readily accessible pinacol coupling products can be used as ketyl radical anion precursors upon simple deprotonation and subsequent C−C-bond homolysis in a reverse pinacol coupling step. The thus generated radical anions might engage as reagents in single-electron reductions[3] or in other radical transformations.

Herein we show that ketyl radical anions generated by reverse pinacol coupling react in the absence of any transition metal with iodoarenes to afford the corresponding alcoholates which upon protonation eventually provide tertiary alcohols.

For initial studies, benzophenone pinacol **1a** and *ortho*-iodoanisole (**2a**) were used as model compounds and reactions were conducted in THF under different conditions. Pleasingly, transformation of equimolar amounts of **1a** and **2a** (slowly added over 1 h) using sodium hydride as a base (4 equiv) at room temperature for 20 h provided 2-methoxyphenyl-diphenyl-methanol (**3aa**) in 48% isolated yield (Table 1, entry 1). As byproducts, diphenylmethanol (**4a**) and benzophenone were obtained in 28% and 3% yield, respectively. An improved yield (68%) was obtained upon adding the aryl iodide **2a** in one portion (Table 1, entry 2). Conducting the coupling at 60 °C led to a slightly lower yield (Table 1, entry 3), and changing the amount of base revealed that the best result is achieved with 5.6 equiv of NaH (Table 1, entries 4−6). We found that a 1.4-fold excess of **1a** with respect to **2a** provides the highest yield and that coupling works best at a concentration of 0.33 M (Table 1, entries 6−10).

The base was varied next. With Na-hexamethyldisilazide (NaHMDS) in place of NaH, the target product **3aa** was not formed and the starting material **2a** was recovered in 36% yield along with 3% of **4a** (Table 1, entry 11). Li-hexamethyl-disilazide (LiHDMS) provided a similar result (Table 1, entry 13). With K-hexamethyldisilazide (KHMDS) a significant amount of **4a** was obtained; however, **3aa** was not identified in the crude reaction mixture (Table 1, entry 12). NaHBEt₃ provided **4a** in 74% yield and target **3aa** was not identified (Table 1, entry 14). Using elemental sodium, **3aa** was formed in 4% yield along with 46% of **4a**. Based on these screening studies we can conclude that NaH is the best base for this reaction.

With the optimized reaction conditions in hand, we then turned to investigate the scope with respect to the aryl iodide component keeping pinacol **1a** as the reaction partner (Scheme 2). As expected, the 2-ethoxy-substituted iodobenzene provided **3ab** in a good yield (70%). 2-Iodothioanisole **2c** was also a

Table 1. Reaction Optimization


entry	base (equiv)	1a (equiv)	3aa (%)[a]	4a (%)[a]
1[b]	NaH (4.0)	1.0	48[c]	28[c]
2[d]	NaH (4.0)	1.0	68	8
3[d,e]	NaH (4.0)	1.0	57	7
4[d]	NaH (3.0)	1.0	56	10
5[d]	NaH (5.0)	1.0	65	13
6[d]	NaH (5.6)	1.4	74	20
7[d]	NaH (6.4)	1.6	72	11
8[d,f]	NaH (5.6)	1.4	69	15
9[d,g]	**NaH (5.6)**	**1.4**	**76**	**8**
10[d,h]	NaH (5.6)	1.4	68	7
11[b]	NaHMDS (4.0)	1.0	–	2
12[b]	KHMDS (4.0)	1.0	–	20
13[b]	LiHMDS (4.0)	1.0	–	3
14[b]	NaHBEt₃ (4.0)	1.0	–	37
15[b]	Na (4.0)	1.0	4	23

[a]Reaction conducted with 0.5 mmol of **2a** in 2 mL of THF, and yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b]The pinacol **1a** was first reacted with the base for 2 h, and then **2a** was added using a syringe pump over 1 h. [c]Isolated yield. [d]The pinacol **1a** was first reacted with NaH for 5 min, and then **2a** was added in one portion. [e]The reaction was conducted at 60 °C. [f]3 mL of THF were used. [g]1.5 mL of THF was used. [h]1 mL of THF was used.

suitable coupling partner for this reaction to give **3ac** in moderate yield. Unfortunately, upon using the unsubstituted parent iodobenzene, a complex reaction mixture resulted and the target product could not be isolated. Also 4-methoxy iodobenzene was not a substrate in this reaction indicating that a heterosubstituent at the ortho-position of the leaving group plays an activating role in this transformation. We further found that the substitution reaction does not work on aryl bromides as shown by the failed experiment with 2-methoxy bromobenzene. Interestingly, an ortho-substituent was not required for 1-iodonaphthalene **2d** and the tertiary alcohol **3ad** was isolated in 50% yield. As compared to benzene and its congeners, the π-system in naphthalene is more reactive. Heteroaryl iodides can also be applied as substrates in this reaction. Hence, transformation of **1a** with 2-iodofuran (**2e**), 2-iodopyridine (**2f**), and 1-iodoisoquinoline (**2g**) afforded the alcohols **3ae**, **3af**, and **3ag** in 49%, 44%, and 40% yield, respectively. However, 2-iodopyridine and 3-iodopyridine were not suitable for this reaction, again indicating the importance of a coordinating functionality in the ortho-position to the I-substituent. To our delight, 2-iodothiophene **2h** worked very well and the alcohol **3ah** was isolated in 83% yield. Good results were also achieved with 2-iodobenzothiophene **2i** and 4-iododibenzothiophene **2j** as iodoarene components in the reaction with benzophenone pinacol **1a** to provide **3ai** and **3aj** in good yields.

We then explored the scope of the novel transformation varying the pinacol component **1** using iodoarene **2a** as a reaction partner. We were pleased to see that the symmetrical pinacols **1b** and **1c** worked in this sequence and products **3ba** and **3ca** were isolated in 58% and 65% yield, respectively (Scheme 3). The unsymmetrical pinacols **1d**, **1e**, and **1f** worked equally well (see **3da**, **3ea**, and **3fa**). 9H,9′H-[9,9′-Bixanthene]-

Scheme 2. Reaction Scope: Variation of the Aryl Iodide[a]
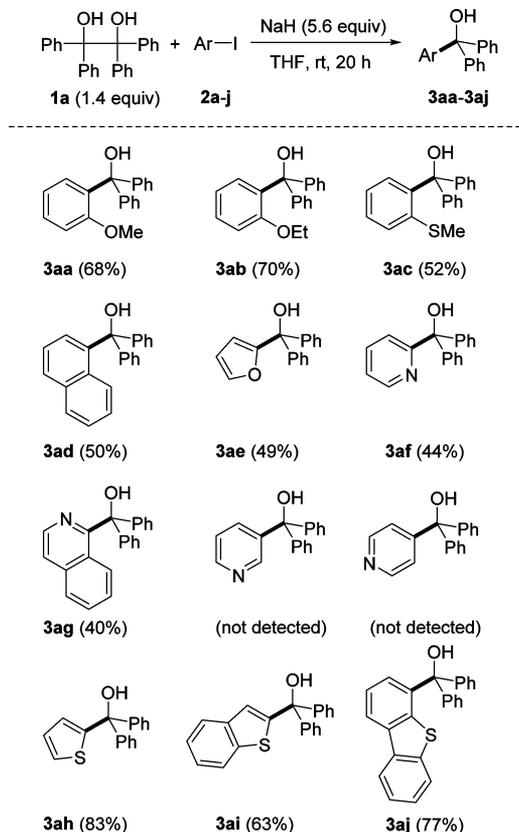
[a]The reaction was conducted using **1a** (1.4 equiv), **2** (0.5 mmol), NaH (5.6 equiv) in 1.5 mL of THF at room temperature for 20 h. Isolated yields are given.

Scheme 3. Reaction Scope: Variation of the Pinacol
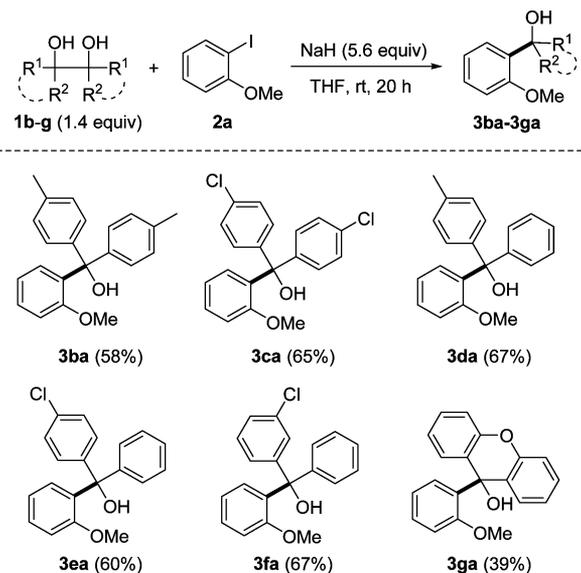
9,9′-diol (**1g**) could also be applied in this transformation yielding **3ga** in 39% yield. However, with the pinacol derived from acetophenone, coupling did not occur and the target product was not identified in the crude reaction mixture.

In order to investigate the reaction mechanism, we ran additional mechanistic experiments. To check whether free aryl radicals are involved in these processes, aryl iodides **2k**−**2m**

were tested. To our surprise, products of type **5** derived from a 5-*exo*-aryl radical cyclization were not identified and the tertiary alcohols **3ak**−**3am** were obtained in 55−62% yield (Scheme 4).
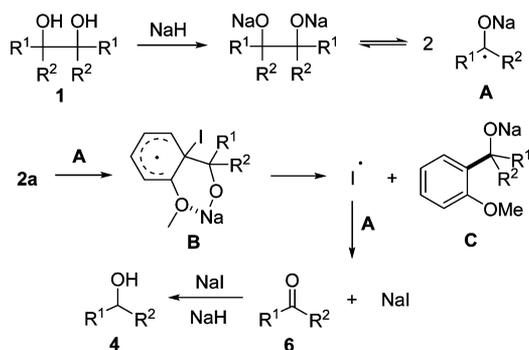
Scheme 4. Mechanistic Studies
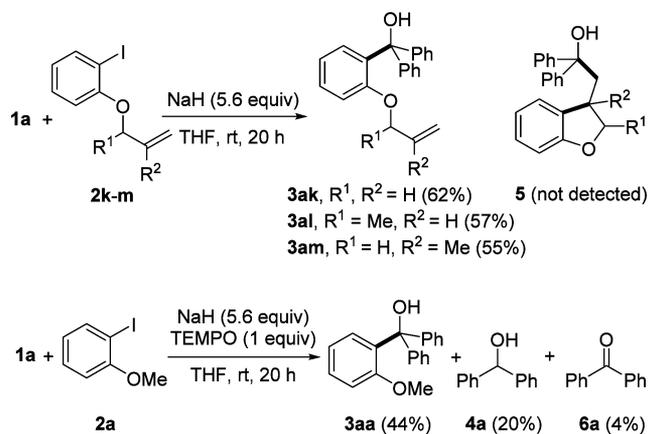
These results show that free aryl radicals are not generated in these transformations. Moreover, in the reaction of **1a** with aryl iodide **2a**, the presence of TEMPO (1 equiv) did not suppress the coupling and **3aa** was formed albeit in a slightly lower yield. In this experiment the byproducts **4a** and benzophenone (**6a**) were obtained in 20% and 4% yield, respectively. Also this result indicates that a free aryl radical is likely not formed.

Based on these experiments we propose the following mechanism for the overall process as exemplified for the reaction of pinacols **1** with iodoarene **2a** (Scheme 5).

Scheme 5. Suggested Mechanism

Deprotonation of **1** with NaH gives the corresponding Na-pinacolate which is in equilibrium with its Na-ketyl radical anion **A**.[2c] The blue color of the ketyl radical anion **A** in THF is indeed observed after deprotonation of the pinacols. We assume that this radical anion **A** then adds to the arene of **2a**, likely assisted by complexation of the sodium cation with the ether O atom of **2a**, to generate the cyclohexadienyl radical **B**. Fragmentation of the iodine atom affords the product Na-alcoholate **C**. Note that homolytic ipso-substitutions with halogen atoms as leaving groups are known.[4] The iodine atom then gets reduced by the ketyl radical anion **A** to give ketone **6** along with NaI. As recently shown by Chiba et al., the NaH/NaI-couple can act as a reducing reagent,[5] and in a separate experiment we could show that benzophenone gets reduced by NaH/NaI under the reaction conditions. Hence, formation of

alcohol **4** as a major byproduct can be explained by this reduction.

In summary, we have presented transition-metal-free C−C bond formation of Na-ketyl radical anions with various aryl and heteroaryl iodides to provide tertiary Na-alcoholates. The intermediate ketyl radical anions are readily generated by thermal reverse pinacol coupling of the corresponding Na-pinacolates. NaH turned out to be best suited for deprotonation of the pinacols. Interestingly, free aryl radicals are not involved in these transformations and C−C bond formation is suggested to occur via homolytic aromatic ipso-substitution with the iodine atom acting as a radical leaving group. These reactions are experimentally easy to conduct and occur under mild conditions at room temperature. NaH used as a reagent is commercially available and not costly.

■ ASSOCIATED CONTENT

S **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02184.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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