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Four Pathways in Radical Alkylation of Isocyanide with Simple Alcohol

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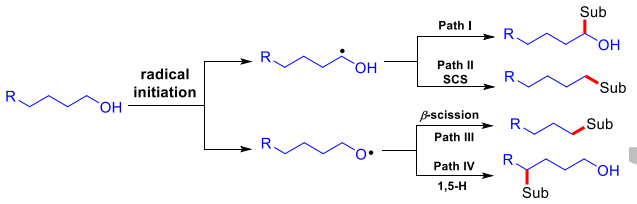
Abstract: We demonstrated herein the four modes in free-radical C-C formation reaction of isocyanide with alcohol. The experimental results and DFT calculation revealed when and why one model opens. It would be instructive and valuable for radical alkylation with alcohol in organic synthesis.

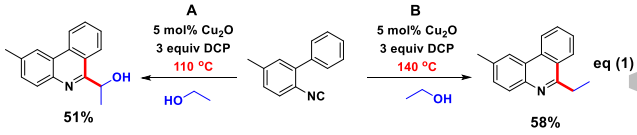
Keywords: Free-radical; C-C bond formation; Alcohol; Isocyanide; DFT calculation

The radical alkylation using alcohol as the alkyl source represents one of the most sustainable and attractive conversions in synthetic organic chemistry.[1] There are usually four pathways in these transformations (Scheme 1). Path I is the hydroxyalkylation via a C-centered radical intermediate by direct hydrogen-atom-transfer (HAT) of the α-hydroxyl C-H, which has been well-developed by Tu,[2] Han and Pan,[3] and Liu [4] et al.[5] A dehydroxylative alkylation via spin-center-shift (SCS)[6] from the same intermediate represents the second process, which is widely found in biological system. Besides, an alkoxyl radical intermediate could be often formed via one-electron oxidation followed by deprotonation of alcohol.[7] Path III is a decarbonylative alkylation via a β-fragmentation of the alkoxyl radical.[8] The last model is a *δ*-hydroxyalkylation via a 1,5-H shift.[9] Recently, a variety of highly efficient systems involving one of these processes have been developed. However, several interesting questions were raised. For example, what's the relationship between each other? What condition leads to what model? To the best of our knowledge, studies focused on answering these questions have never been reported so far. Herein, we wish to report a first study on the connection between these pathways via a Cu(II)-catalyzed radical alkylation of diaryl isonitrile with alcohol.[10]



Scheme 1. Four major models in radical alkylation with alcohol.

In 2014, we reported a radical-triggered hydroxyalkylation of isocyanide with alcohol (eq. 1, path A).[4c] Accidentally we found that a dehydroxylative alkylation occurred while the temperature of reaction was raised to 140 °C (path B). This surprising result stirred up our great interests because both the mechanism and the potential application in synthetic chemistry would be attractive.



Initially we evaluated the substrate scope after modification of the reaction conditions (Table 1 and 2). As illustrated in Table 1, a series of 6-ethylphenanthridines can be smoothly synthesized in moderate to good yield (1-12).

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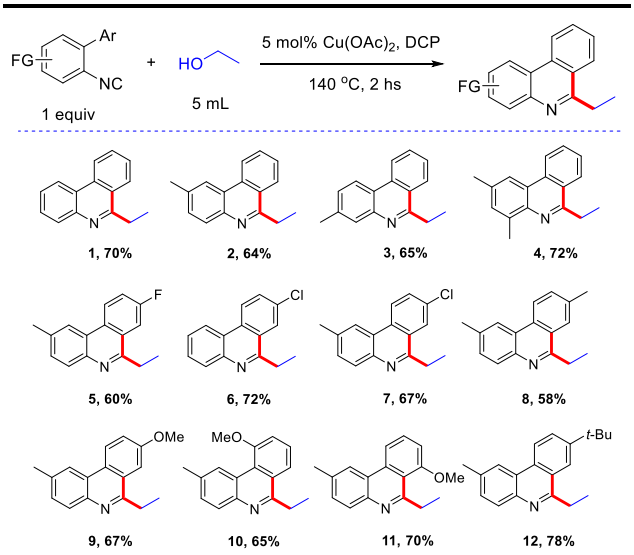
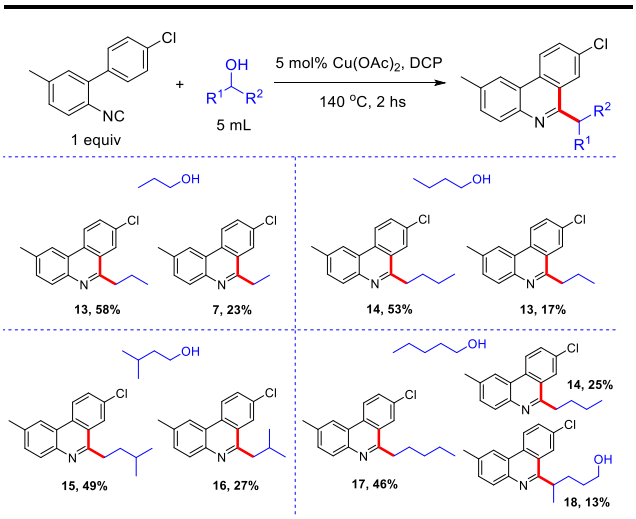
Table 1. Radical alkylation of isocyanide with ethanol.[a]

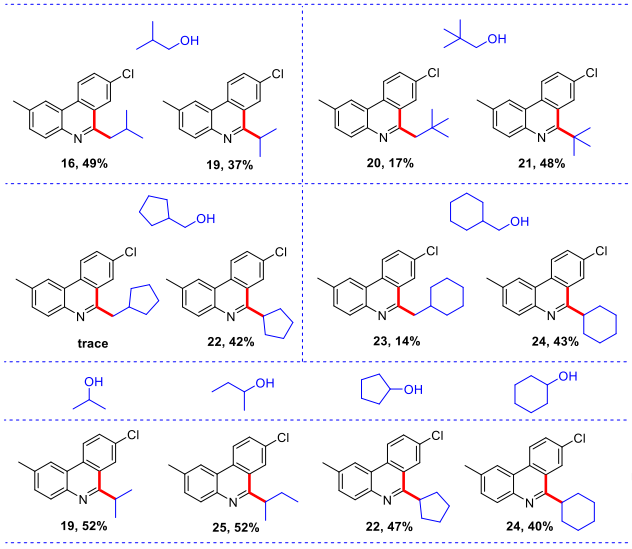


[a]Typical reaction conditions: isocyanide (1 equiv., 0.1 mmol), $Cu(OAc)_2$ (5 mol%, 0.005 mmol), DCP (dicumyl peroxide) (5 equiv., 0.5 mmol), alcohol (5 mL), 140 °C (measured temperature of oil bath), sealed tube, 2 h., unless otherwise noted, isolated yield.

On the other hand, various simple alcohols afforded the corresponding alkylated phenanthridines under the typical conditions (Table 2). Interestingly, along with the dehydroxylative alkylated product, a decarbonylative alkylation phenanthridine was also isolated (13-25). It is noteworthy that 1-pentanol gave 3 main products 14, 17 and 18. In addition, the more β-substituents have in the primary alcohols, the more decarbonylative products can be obtained. Secondary alcohols only gave the dehydroxylative alkylation phenanthridines (19-25).

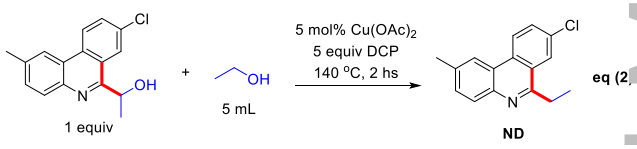
Table 2. Radical alkylation of isocyanide with alcohol.[a]



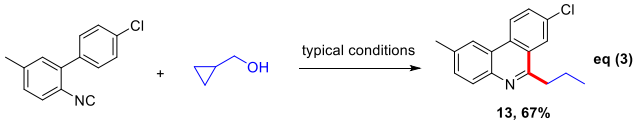


[a]Typical reaction conditions: isocyanide (1 equiv., 0.1 mmol), $Cu(OAc)_2$ (5 mol%, 0.005 mmol), DCP (5 equiv., 0.5 mmol), alcohol (5 mL), 140 °C (measured temperature of oil bath), sealed tube, 2 h., unless otherwise noted, isolated yield.

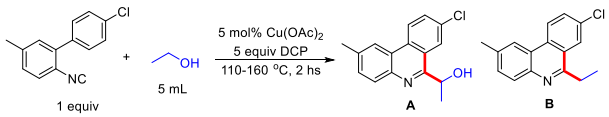
And then a set of control experiments were carried out to study the detailed mechanism. Firstly, it has been confirmed that the hydroxyalkylated phenanthridine can not convert into dehydroxylative product under the reaction conditions (eq. 2).



Surprisingly, reaction of cyclopropyl methanol with isonitrile led to product **13** in 67% yields under the typical conditions (eq. 3). It seems undergo a ring-opening decarbonylative alkylation, but the detailed process is not clear.



Next we examined the relationship between temperature variation and the yields of the products (Figure 1). It can be seen from Figure 1 that **A** was the major product when the temperature was lower than 130°C. Product **B** became dominant while the temperature higher than 130°C.



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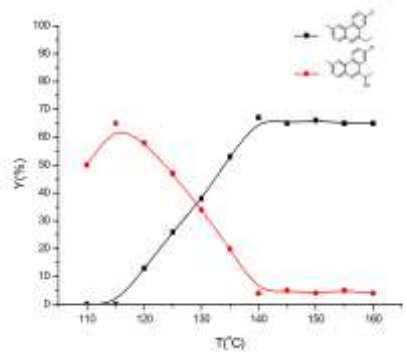

Figure 1. Diagram of yields with temperature variation.

In order to investigate the possible relationship between the typical four models of alcohol involved free radical reactions, the following experiments were carried out (Figure 2). As expected, four products have been obtained during the temperature variation (70-160ºC). Products A and D appeared at 80ºC while B and C were observed until 110ºC. The varying trends of A and B are similar to that of ethanol.

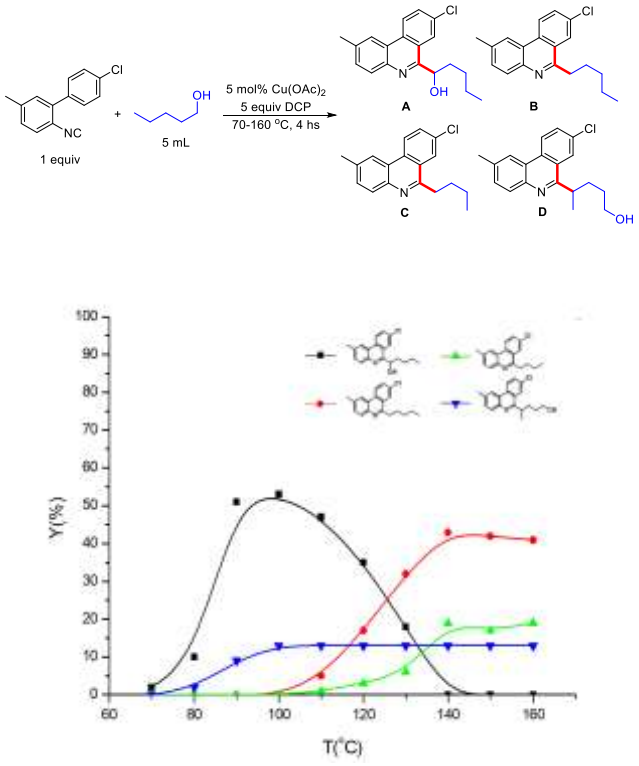

Figure 2. Diagram of yields with temperature variation.

Furthermore, spin-trapping combined with electron paramagnetic resonance (EPR) experiments were designed to investigate the mechanism in details (Figure 3). It can be seen from Fig. 3 that two radical intermediates were clearly recorded by EPR (triplet and sextet). The triplet signal should belong to di-*tert*-butylnitroxide (DTBN) radical, which was formed by dimerization of the spin trap 2-methyl-2-nitroso-propane (MNP). And the sextet signal should belong to the 2-hydroxylethyl-*tert*-butylnitroxide radical (a_N = 16.25 G; a_H = 3.85 G). It indicates that the α-hydroxy-ethyl radical should be formed in this reaction.

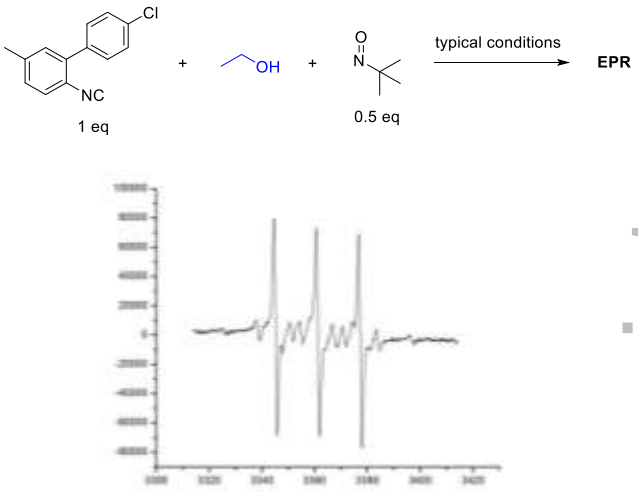

Figure 3. Spin-trapping and EPR studies.

Based on these results and previous literatures, we proposed the possible mechanisms for the free-radical alkylation of biarylisonitriles. As demonstrated in Scheme 2 that four main pathways might be involved in the reactions. Path I and path II start with the α-hydroxyl-C-centered radical **A**, which was generated via hydrogen-atom transfer (HAT) from alcohol. Radical addition of **A** to isocyanide and then cyclization afforded radical **C**. Direct HAT or deprotonation followed by single-electron oxidation gave **P1**. The intermediate **C** would convert into **D** at a higher temperature via a spin-center shift (SCS) process.[6] Subsequently, hydrogen abstraction of alcohol by **D** led to **P2**. On the other hand, an alkoxyl radical **B** would produce under the conditions. β-Fragmentation of **B** gave radical **E** by release of HCHO, which is Path III. Then **P3** was obtained via a similar process to Path I. The last path began with radical **G** which was formed by a 1,5-H atom shift of **B**. Next a radical addition/cyclization cascade process afforded **H**, which then gave **P4** via a dehydrogenative rearomatization process.

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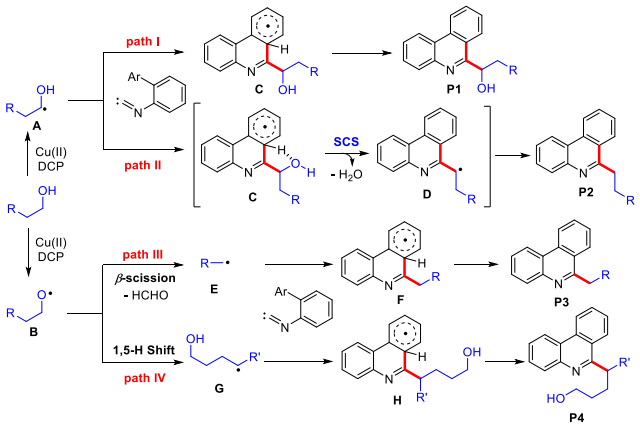

Scheme 2. Suggested mechanism.

Finally, the computed Gibbs free energy profile for the four pathways in reaction of 1-pentanol (1) with 2-isocyano-5-methyl-1,1'-biphenyl (2) have been carried out (Figures 4-6, see also the SI). It can be seen from Figure 4 that the rate-determining step (RDS) in path I and path II is HAT from alcohol to radical A (the barrier is 19.1 kcal/mol, which is consistent with the KIE result.) and SCS (the barrier is 35.9 kcal/mol) respectively. In cases of path III and IV, the RDS is β-fragmentation (Fig. 5, the barrier is 17.0 kcal/mol) and the 1,5-H shift (Fig. 6, the barrier is 14.6 kcal/mol) respectively. Thus, it is not difficult to understand when and why one pathway occurs. At a relatively lower temperature, the processes I, III and IV which have relatively lower energetic barrier all could happen. Path II began to dominate the reaction with the increasing of the temperature. Nevertheless, P1 and P2 were always the major product over P3 and P4. It should be due to the radical stability and polarity. The SOMO-p (lone pair) delocalization might make radical A more stable than the alkoxy radical B and its derivatives F and H.[4d] Besides, nucleophilic C-centered radical A could add to electrophilic isocyanide directly. In contrast, electrophilic alkoxy radical B couldn't react with isonitrile unless it converted into radical F via β-fragmentation or radical H by 1,5-H shift. At a high temperature, P2 became the predominant product might be attributed to the entropy effect.

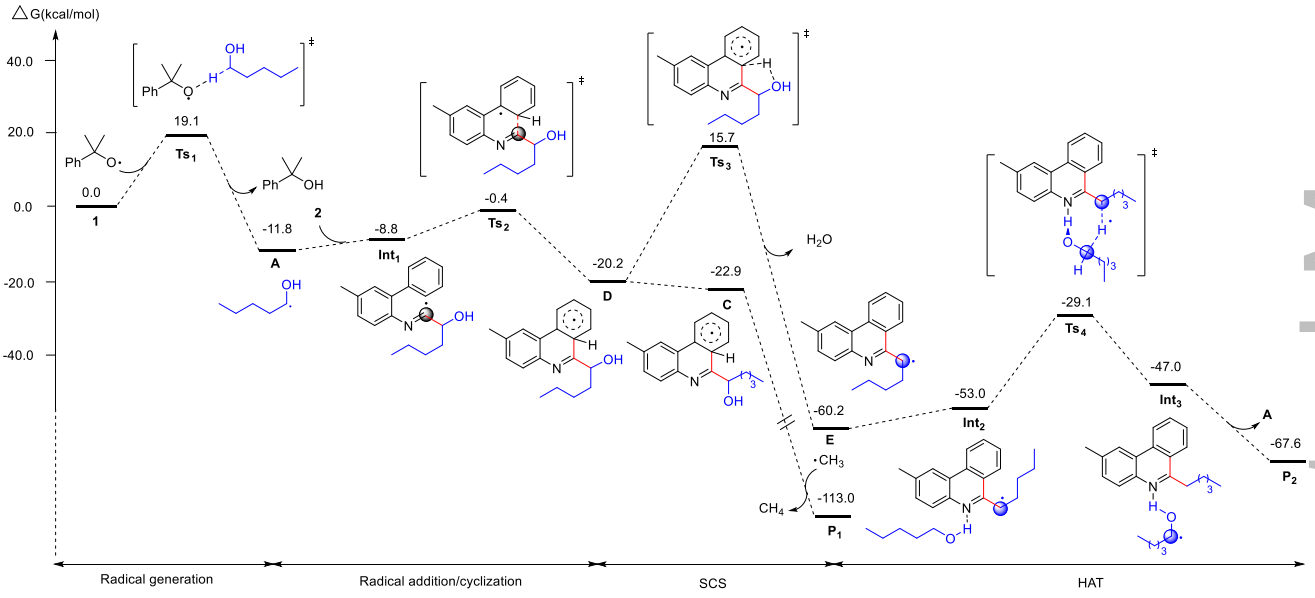

Figure 4. The Computed Gibbs Free Energy Profile for Path I and II.

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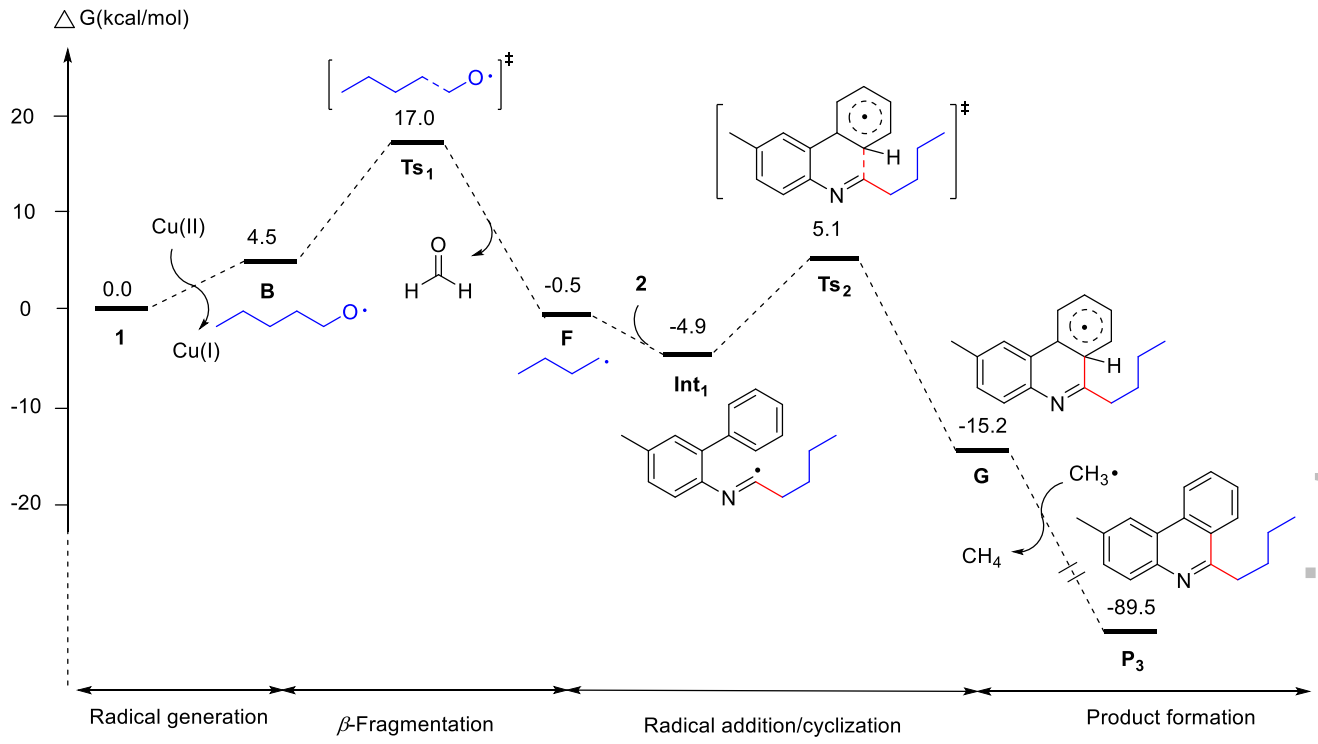

Figure 5. The Computed Gibbs Free Energy Profile for Path III.

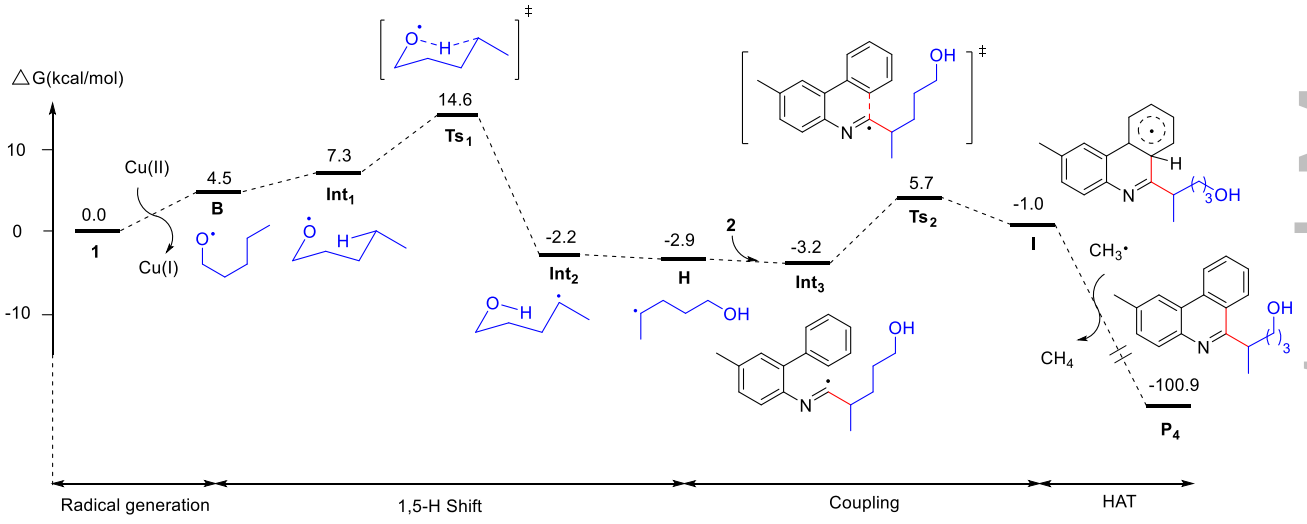

Figure 6. The Computed Gibbs Free Energy Profile for Path IV

In summary, a free-radical alkylation of isocyanide with simple alcohol was demonstrated, which showed the diversity of radical addition reaction of isonitriles.[11] We found that there were four reaction modes that would afford four different products. Then we investigated these pathways in details. The experimental and computed results could explain when and why one pathway occurs well. Hence it might be instructive and valuable for field of radical C-C bond formation with alcohol. Continuous studies on controlled radical alkylation of other molecules with alcohol are ongoing in our lab.

Experimental Section

General procedure: A mixture of biarylisonitriles (1 equiv., 0.1 mmol), $Cu(OAc)_2$ (5 mol %, 0.005 mmol), DCP (5 eq, 0.5 mmol) and alcohols (5 mL) was heated under nitrogen at 140 °C (this temperature is measured outside of the reaction mixture, it is the temperature of the oil bath) for about 2 h in a sealed tube (25 mL). After the reaction finished, the mixture was evaporated under vacuum and purified by column chromatography to afford the desired product.

Acknowledgements

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