

Atf İçin: Korkmaz A. Copper-Catalyzed Electrophilic Amination of Diarylcadmium Reagents Utilizing Acetone *O*-(4-chlorophenylsulphonyl)oxime and Acetone *O*-(2-naphthylsulphonyl)oxime as Amination Agent. İğdır Üniversitesi Fen Bilimleri Enstitüsü Dergisi, 11(3): 2102-2111.

To Cite: Korkmaz A. Copper-Catalyzed Electrophilic Amination of Diarylcadmium Reagents Utilizing Acetone *O*-(4-chlorophenylsulphonyl)oxime and Acetone *O*-(2-naphthylsulphonyl)oxime as Amination Agent. Journal of the Institute of Science and Technology, 11(3): 2102-2111.

Copper-Catalyzed Electrophilic Amination of Diarylcadmium Reagents Utilizing Acetone *O*-(4-chlorophenylsulphonyl)oxime and Acetone *O*-(2-naphthylsulphonyl)oxime as Amination Agent

Adem KORKMAZ^{1*}

ABSTRACT: In this study, a CuCN catalyzed process of the diarylcadmium compounds by electrophilic amination method was developed using novel acetone *O*-(4-chlorophenylsulfonyl)oxime and acetone *O*-(2-naphthylsulfonyl)oxime. Herein, it has been demonstrated that primary arylamines can easily be obtained with good yields at room temperature by CuCN catalyzed amination of diarylcadmium reagents. It was settled down that the yield of primary arylamines depended strongly on the steric and electronic effects of organocadmium reagent and amination agent. In both amination reagents, meta-substituted arylamines were obtained in higher yields than para-substituted aryl amines. All reactions involving organocadmiums were carried out under an argon atmosphere by standard syringe/cannula methods. Amines as reaction products were separated from the reaction mixture as benzamide derivatives and purified and melting points, ¹H NMR analysis determined their accuracy.

Keywords: Electrophilic amination, diarylcadmium reagents, benzamides, ketoximes, copper catalysis

INTRODUCTION

Transition-metal-catalyzed C-N bond-forming is one of the most considerable scaffold transformations in organic synthesis for the various aryl amines. For these reasons, various procedures have been evolved for aryl C-N bond formation, for example, the reduction of aromatic nitro compounds (Jayapal et al., 2018), nucleophilic aromatic substitution (Shoji et al., 2019), Ullmann Reaction (Ullmann, 1903; Wang et al., 2019), Buchwald-Hartwig method (Snieckus and Kölmel, 2019), Chan-Lam coupling (Campbell Brewer, 2019) (Figure 1). The investigated methods relating to aryl amines let obtaining amines in good yields, but these methods have significant drawbacks, which are a high temperature, long reaction condition, high pressure, expensive or specific catalysts, and ligands.

Especially in recent years, Yu and coworkers have identified electrophilic amination of arylboronic acids with azo compounds using Cp*Rh(III) catalyst, which is quite expensive (Lau et al., 2016). In addition, Kürti and co-workers accomplished the various arylmetallic reagents with NH-oxaziridine as an amination agent with managed to implement long reaction time and low temperature (-78°C) conditions by electrophilic amination reaction (Behnke et al., 2018). Furthermore, Sato and co-workers described the methodology for preparing primary aryl amines, using an N-methoxyamine and triarylboroxin by copper-catalyzed electrophilic amination 85°C in 24h (Fukami et al., 2018).

Besides, Olah and his co-workers unveiled an aromatic C-H electrophilic amination method to construct primary anilines. They managed to obtain various functionalized primary anilines, by using NaN₃ as amination reagents in the presence of boron trifluoride monohydrate at 55 °C temperature between 12 and 72 hours reaction conditions (Prakash et al., 2016). Moreover, Smith and their co-worker used N,N-dialkyl-O-benzoylhydroxylamines as an aryl C-N amination agent with organolithium employing siloxane transfer agent (Nguyen and Smith, 2013). The electrophilic amination reaction was achieved effectively in the presence of CuI as catalyst (10 mol%) and dpca as an additive (10 mol%).

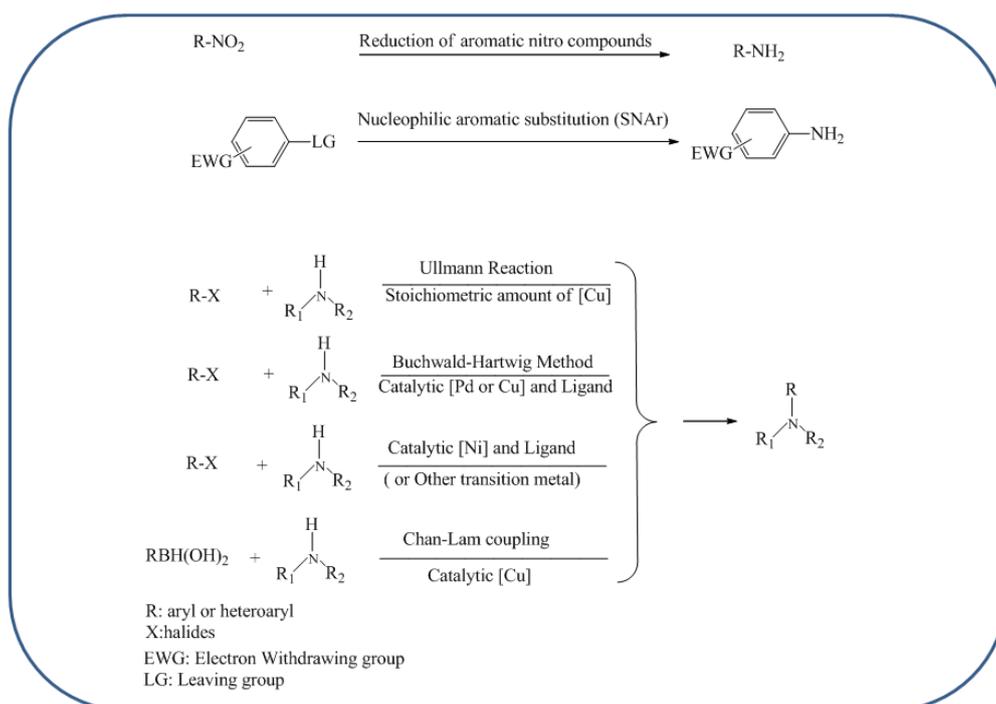


Figure 1. C-N bond formation methods

1.92 (s, 3H, CH₃). ¹³C-NMR spectrum (100 MHz, DMSO-d₆) δ (ppm): 165.36 (R¹R²C=N), 140.46, 134.33, 130.22, 129.24 (Ar-C), 21.62, 16.96 (R-C).

Acetone *O*-(2-naphthylsulphonyl) oxime (**2**), (2.161 g, 60%, mp 92-95 °C); ¹H NMR spectrum, (400 MHz, CDCl₃) δ (ppm): 8.56 (s, 1H, naphthyl-H), 7.93-7.90 (m, 4H, naphthyl -H), 7.68-7.59 (m, 2H, naphthyl -H), 1.98 (s, 3H, CH₃), 1.89 (s, 3H, CH₃). ¹³C-NMR spectrum (100 MHz, DMSO-d₆) δ (ppm): 165.10 (R¹R²C=N), 135.35, 132.80, 131.93, 130.70, 129.44, 129.30, 129.13, 127.93, 127.58, 123.32 (naphthyl-C), 21.64, 16.95 (R-C).

Amination of Ar₂Cd

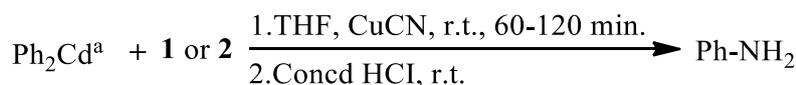
A solution of CdI₂ (0.3662 g, 1 mmol) in anhydrous THF (3 ml) was cooled to -10 °C under an argon atmosphere, and phenylmagnesium bromide (2 mmol) in THF was added dropwise by syringe. The reaction mixture was stirred for an additional 10 min, the cooling bath was removed, and the resulting suspension was allowed to warm to room temperature. To this mixture, CuCN catalyst (1.25–12.5 mmol%) and a solution of **1** (1 mmol) or **2** (1mmol) in dry THF (3 ml) were added.

RESULTS AND DISCUSSION

The optimization conditions of the electrophilic amination reaction with **1** and **2** as amination agents began to implement the different ratios of CuCN catalyst and various reaction times with diphenylcadmium reagent. (Table 1, Entry 1-12). Initially, it was applied **1** as an amination reagent with 2.5 mol% CuCN at room temperature for 90 minutes employing diphenylcadmium reagent and pleasingly, was obtained the desired product in 51% yield (Table 1, Entry 1). Giving the same reaction time, the desired product yield was determined to be 69% by using the catalyst ratio of 7.5 mol% CuCN (Table 1, Entry 2). We determined more or fewer catalyst ratios than 7.5 mol% reduced the yield (Table 1, Entry 3 and 4). Similarly, longer and shorter reaction times than 90 minutes decreased the yield (Table 1, Entry 5 and 6). It was uncovered that the best phenylamine yield was obtained 7.5 mol% CuCN catalysis and 90 minutes utilizing **1** as an amination agent. Similar steps were followed for **2** as animation reagent. Attempts to decrease or increase the amount of CuCN provided an enhancement of the optimal condition for **2**. The best arylamine yield was determined 90 minutes with 10 mol% CuCN catalyst ratio for **2** as amination agent.

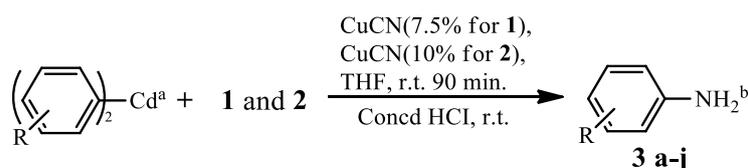
The next step, we explored the scope of the Cu-catalyzed electrophilic amination of various functional diarylcadmium reagents with **1** under the optimized reaction conditions. Diverse diarylcadmium reagents containing electron-donating groups (EDG) and electron-withdrawing groups (EWG) underwent effective coupling with **1** to form the corresponding primary amine derivatives in good yields (Table 2, **3a-j**). In particular, the di(*m*-methoxyphenyl)cadmium reagents smoothly underwent electrophilic amination to provide the desired product in high yield (**3b**).

On the other hand, the di(3,4,5-trimethoxyphenyl)cadmium reagents proceeded with slightly lower efficiency (**3j**). Notably, It was observed that the yield of meta(-Cl)-substituent (**3c**) was higher than the para(-Cl)-substituent (**3a**). Then, we checked-up the use of the other amination agent (**2**) with functional diarylcadmium reagents, focusing on the capacity to achieve the desired product via an easy protocol. Unfortunately, we have found that the copper-catalyzed electrophilic amination efficiency of the diarylcadmium reagents with **2** was generally lower than **1**.

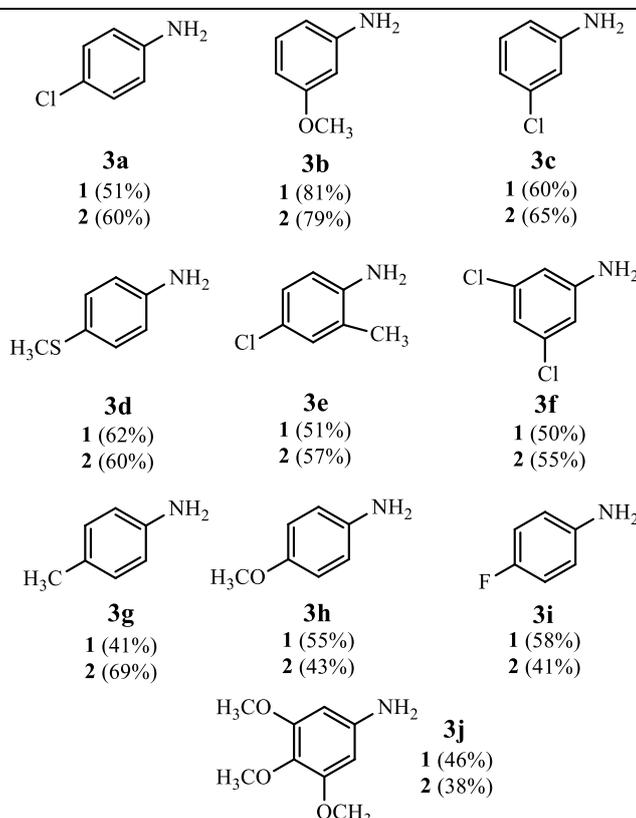
Table 1. The optimization conditions of the CuCN-catalyzed electrophilic amination of Ph₂Cd with **1** and **2**

Entry	Ar	Amination Agent	CuCN(%)	Time(min.)	Yield ^b (%)
1	C ₆ H ₅	1	2.5	90	51
2	C ₆ H ₅	1	7.5	90	69
3	C ₆ H ₅	1	5	90	54
4	C ₆ H ₅	1	10	90	36
5	C ₆ H ₅	1	7.5	60	59
6	C ₆ H ₅	1	7.5	120	37
7	C ₆ H ₅	2	5	90	32
8	C ₆ H ₅	2	2.5	90	34
9	C ₆ H ₅	2	7.5	90	37
10	C ₆ H ₅	2	10	90	51
11	C ₆ H ₅	2	10	120	47
12	C ₆ H ₅	2	10	60	35

^aAr₂Cd/**1**=1. ^bYield of phenylamine was isolated as its N-benzoyl derivatives, and this known compound was identified from its melting point, ¹H NMR analysis.

Table 2. CuCN-catalyzed electrophilic amination of the functional diarylcadmium reagents with **1** and **2**

Structure of Primary Arylamines



^aAr₂Cd/**1**=1. ^bYield of amines were isolated as their N-benzoyl derivatives, and these known compounds were identified from their melting point, ¹H NMR analysis.

Empirical research for this study aims to build up a novel designed method for providing primary amines (Figure 3). Additionally, this research has been designed to determine whether as amination reagents of the acetone *O*-(4-chlorophenylsulfonyl)oxime **1** and the acetone *O*-(2-naphthylsulfonyl)oxime **2** are suitable for electrophilic amination reaction with diarylcadmium reagents. At the same time, part of this study aims to investigate the effectiveness of **1** and **2** as the amination reagents with diarylcadmium reagents in electrophilic amination. Both qualitative and quantitative experimental data were used in this investigation. This paper is exhibited that the primary amines are directly accessible utilizing acetone *O*-(4-chlorophenylsulfonyl)oxime and acetone *O*-(naphthylsulfonyl)oxime as the root of electrophilic nitrogen for electrophilic amination with diarylcadmium reagents.

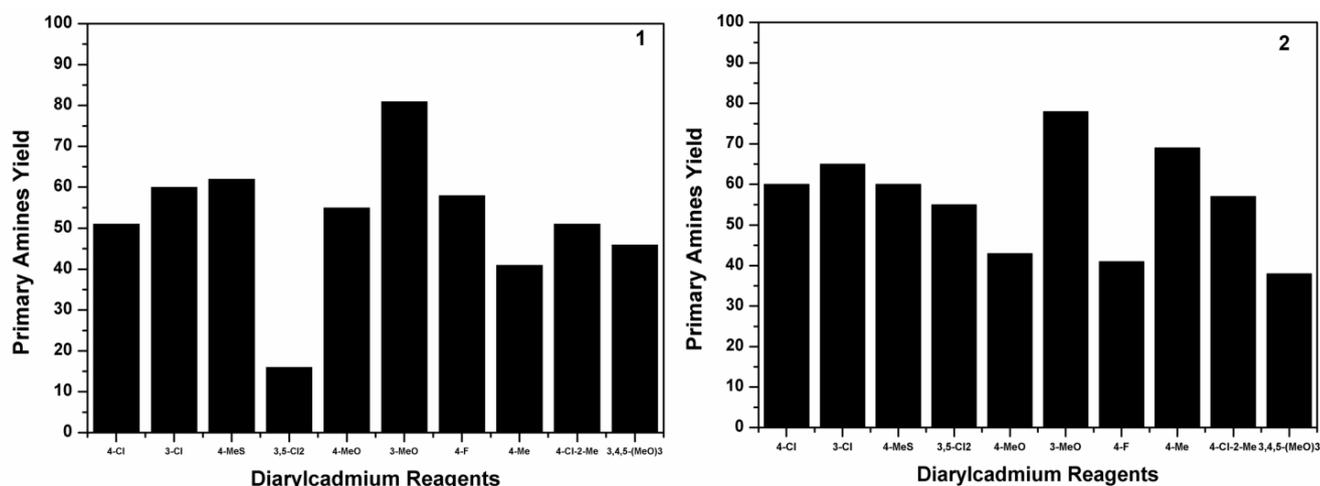


Figure 3. The graph of the various functional diarylcadmium reagents versus the primary amine yields using **1** and **2** as amination agents

A mechanism for CuCN catalyzed electrophilic amination of diarylcadmium compounds has been proposed by using the literature data of organocopper compounds and copper-catalyzed coupling of organozinc reagents in the literature, and explanations have been made considering these mechanisms (Yoshikai and Nakamura 2012; Dzedzic and Spokoyny, 2019). The proposed mechanism for CuCN catalyzed amination of diarylcadmium iodides with ketoximes is given in Figure 4.

The Mechanism Evaluation of Diarylcadmium Reagents with the Same Functional Group in Different Positions

The rate-determining step can prefer oxidative addition or the reductive elimination step in the mechanism depending on the reaction conditions, the nucleophile structure, and the electrophile. Furthermore, both the electronic effects and steric effects of these structures are effective in selecting the rate-determining step (Gonzalez-Perez et al., 2012; Liu and Xi 2019). In the case of the amination of diarylcadmium containing a functional group, it is not possible to give a precise sequence of activity. Steric hindrance and electronegativity can be evaluated where they are performed under the same reaction conditions. Thus, for the diarylcadmium reagents having the same functional group at different positions, the rate-determining step can be estimated as the oxidative addition step or the reductive elimination step thanks to the amine yields obtained. For example, when comparing (4-ClC₆H₄)₂Cd reagent and (3-ClC₆H₄)₂Cd reagent, the yield of 3-Cl substituted reagent had been found to be higher (see Table 2). It has known that the chloro-substituent has the property $-I \gg +M$. Electron-withdrawing (-I) efficiency of the -Cl substituent is more dominant comparing electron-

donating, and responsible for the low activity of the organocadmium reagent. It has known that the chlorine group in the (4-ClC₆H₄)₂Cd structure at the 4-position is greater remote distance from the position than the chlorine group in the (3-ClC₆H₄)₂Cd structure. This event affects the nucleophilic character of the functional diarylcadmium reagent. In this case, the efficiency of the (4-ClC₆H₄)₂Cd reagent should have been more active because of a weak electron-withdrawing feature compared to 3-Cl substituent. But, the experimental data has shown that the (3-ClC₆H₄)₂Cd reagent gave a better amine yield than the (4-ClC₆H₄)₂Cd reagent. In experiments conducted under the same reaction conditions, if there is an opposite situation to the value of the electronic effect, it is inevitable to interpret a steric effect in the evaluation of the mechanism. The 3-position substituent may be said to have a more significant steric effect than the 4-position substituent, because it is more branched, i.e., bulky. Simultaneously, it is possible to say that the substituent at the 4-position has a more linear structure than the 3-position. For these reasons, since the 3-position substituent is bulky, there is going to be a steric hindrance in the reductive elimination step. Thereby, it is considered to induce unstabilize the resulting transition state complex. Due to the instability of the transition state complex at the reductive elimination step, the complex is considered rapidly going to degrade. In this instance, the reductive elimination step would be more straightforward, and the resulting product yield going to increases. As can be seen in the experimental data, it was seen that these theoretical notions were supported.

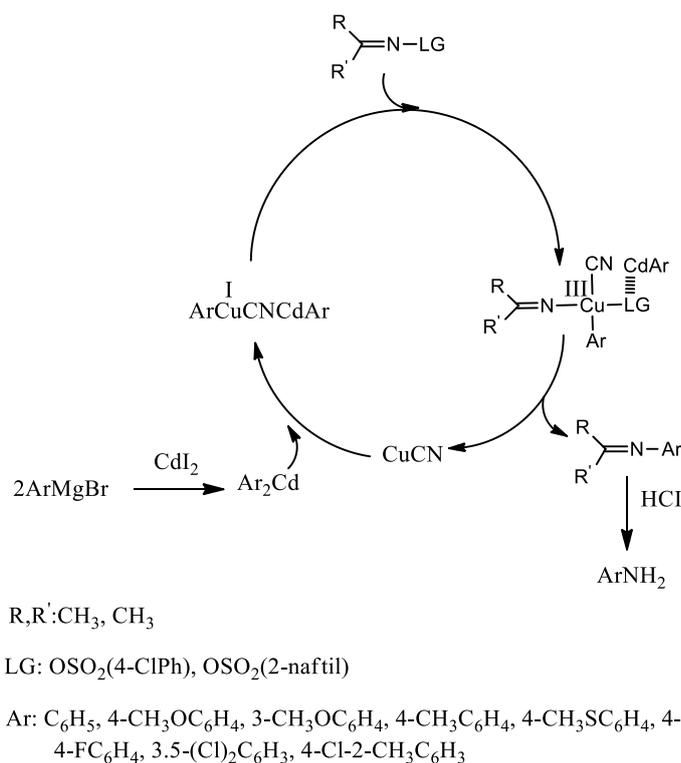


Figure 4. Proposed CuCN catalyzed reaction of diarylcadmium reagents

Also, It has been evaluated the methoxy group, one of the other functional groups we used in the reaction mechanism. It has known that the electronic effects of the methoxy group have the properties $-I \ll +M$. Wherein the mesomeric effect is known to be more effective than the electronegativity effect for the methoxy group. By position, the 4-methoxy group contributes more mesomeric additive to the phenyl ring than the 3-methoxy structure. Therefore, the diarylcadmium reagent activity of the 4-methoxy group should be higher than the 3-methoxy group. Unfortunately, it was observed that the

yield of the 3-substituted position higher than the 4-substituted position (See Table 2). It was explained this yield difference as follows.

Looking at the structures, the structure of the meta-substituent has appeared to be more angled than the para-substituent. The structure of the para-substituent has a more suitable linear form than the meta-substituent. Hereby, the meta-substituent diarylcadmium reagent at the reductive elimination step causes instability in the intermediate structure due to the steric hindrance. The intermediate complex owing to the unstable structure has thought to broke down fast and facilitate the product's formation as primer amine. As can be seen in the experimental data, it has been seen that these theoretical concepts are supported in both chlorine and methoxy functional groups.

The Evaluation in terms of the Leaving Group of the Amination Nitrogen Source in the Reaction Mechanism

A part of this study's objective was to understand the effect of the scaffold structure of **1** and **2** amination agents on the reaction mechanism in the electrophilic amination reaction with diarylcadmium reagents. According to the proposed mechanism, copper nucleophile acts on the electrophilic nitrogen of ketoxime as an amination agent in the first step and locates the nitrogen by separating the leaving group. In this case, it is possible to say that if the leaving group's stability increases, we can say that it is better to leave. The sulfonate group is known to stabilize by dispersing the negative charge on resonance and, as a result, is an excellent leaving group. Accordingly, the electron-withdrawing group in the scaffold structure facilitates this resonance, while the electron-donating groups will slow down.

When we look at the stability of the leaving group at **1** and **2**, it can be stated that the chlorine in the structure of the **1** increases the stability of the leaving group after leaving, thereby increasing the arylamine yield. However, it can be said that the stability of the naphthyl group bound to the sulphonate in the **2** after being separated has a considerable effect compared to the chlorophenylsulfonate group. Because, the naphthyl moiety has a resonance character that negative charges becomes distributes very well. It has known that there are usually multiple conditions affecting the reaction mechanism such as a steric effect for naphthyl moiety. In that case, It could be talking about the steric effect in the reaction mechanism. It was understood from the resulted arylamine yields compared to **1** that the naphthyl group's resonance stability was not more effective than the steric effect. Therefore, it is more appropriate to say that most of the efficacy of **1** and **2** are more affected by steric hindrance in the oxidative addition step rather than the leaving group.

While the transition state complex is formed in the oxidative addition step, it is thought to be difficult to form due to the naphthyl group which is the steric barrier in **2**. Therefore, the transition state complex caused to be more unstable, resulting in decreases in aryl amine yield. It has been explained why the effectiveness of the amination reagent (**2**) to which the naphthyl group is attached is low. Indeed, empirical observations supported these explanations.

CONCLUSION

Given the easy preparation of diarylcadmium compounds, the mild reaction conditions, the ease of product purification, and the Cd's recovery, this method comprises a useful application to reach diverse primary arylamines. Furthermore, It has been determined that the electrophilic source **1** is a more effective amination reagent than amination agent **2** for diarylcadmium reagents. Moreover, the structure of the substrate (especially the stability of the leaving group and steric effect), the steric and electronic effect of the functional group bound to the diarylcadmium reagent were observed to affect

the reaction efficiency. The nucleophile and electrophile structure depending on the reaction conditions has been understood that the rate-determining step affects at oxidative addition or reductive elimination. As a result, it is possible to say that these studies will be a driving source for the electrophilic amination reaction of organocadmium reagents. It can be achieved a good yield of the primary amines by adjusting the amination reagent and organocadmium reagent framework structure.

ACKNOWLEDGEMENTS

The author thanks Muş Alparslan University Research Foundation (grant no. BAP-17-TBMY-4901-01), which provides financial support for this study.

Conflict of Interest

The article author declare that there is no conflict of interest.

Author's Contributions

I hereby declare that the planning, execution, and writing of the article were done by me as the sole author of the article

REFERENCES

- Aponick A, Buzdygon RS, Tomko R J, Fazal AN, Shughart EL, McMaster DM, Wigal CT, 2002. Regioselective organocadmium alkylations of substituted quinones. *The Journal of organic chemistry*, 67(1): 242-244.
- Behnke NE, Kielawa R, Kwon DH, Ess DH, Kürti L, 2018. Direct Primary Amination of Alkylmetals with NH-Oxaziridine. *Organic letters*, 20(24): 8064-8068.
- Barber HJ, 1943. Cuprous cyanide: a note on its preparation and use.
- Campbell Brewer A, Hoffman PC, Martinelli JR, Kobierski ME, Mullane N, Robbins D, 2019. Development and Scale-Up of a Continuous Aerobic Oxidative Chan–Lam Coupling. *Organic Process Research & Development*, 23(8): 1484-1498.
- Daşkapan T, 2006. Preparation of primary arylamines via arylzinc chlorides in good yields. *Tetrahedron letters*, 47(17): 2879-2881.
- Daşkapan T, Koca S, 2010. Highly efficient catalytic system for electrophilic amination of arylzinc reagents. *Applied Organometallic Chemistry*, 24(1): 12-16.
- Daşkapan T, Yeşilbağ F, Koca S, 2009. Cosolvent promoted electrophilic amination of organozinc reagents. *Applied Organometallic Chemistry*, 23(6): 213-218.
- Daşkapan T, Cengiz M, 2009. Grignard Reaktiflerinin Aseton *O*-(2, 4, 6-trimetilfenilsülfonyl) oksim ile Elektrofilik Aminasyonuyla Arilaminlerin Sentezi. *Süleyman Demirel Üniversitesi Fen Bilimleri Enstitüsü Dergisi*, 12(1): 9-12.
- Daşkapan T, Çiçek S, 2017. High yielding electrophilic amination method for arylcopper reagents. *Synthetic Communications*, 47(9): 899-906.
- Daskapan T, 2011. Synthesis of Amines by the Electrophilic Amination of Organomagnesium, Zinc, Copper, and Lithium Reagents. *ChemInform*, 42(38): no.
- Daşkapan T, Korkmaz A, 2016. Aryl CN bond formation by electrophilic amination of diarylcadmium reagents with *O*-substituted ketoximes. *Synthetic Communications*, 46(9): 813-817.
- Dziedzic RM, Spokoyny AM, 2019. Metal-catalyzed cross-coupling chemistry with polyhedral boranes. *Chemical communications*, 55(4): 430-442.
- Erdik E, Daşkapan T, 2002. Can we aminate Grignard reagents under Barbier conditions? *Tetrahedron letters*, 43(35): 6237-6239.

- Fukami Y, Wada T, Meguro T, Chida N, Sato T, 2016. Copper-catalyzed electrophilic amination using *N*-methoxyamines. *Organic & biomolecular chemistry*, 14(24): 5486-5489.
- Gonzalez-Perez AB, Alvarez R, Faza ON, de Lera AR, Aurecochea JM, 2012. DFT-Based Insights into Pd–Zn Cooperative Effects in Oxidative Addition and Reductive Elimination Processes Relevant to Negishi Cross-Couplings. *Organometallics*, 31(5): 2053-2058.
- Jayapal M, Jagadeesan H, Shanmugam M, Murugesan S, 2018. Sequential anaerobic-aerobic treatment using plant microbe integrated system for degradation of azo dyes and their aromatic amines by-products. *Journal of hazardous materials*, (354): 231-243.
- Jiang F, Ni C, Hu J, 2017. Efficient nucleophilic difluoromethylation of aldehydes with (phenylsulfonyl) difluoromethylzinc and (phenylsulfonyl) difluoromethylcadmium reagents. *Journal of Fluorine Chemistry*, (198): 67-75.
- Lau YF, Chan CM, Zhou Z, Yu WY, 2016. Cp* Rh (III)-catalyzed electrophilic amination of arylboronic acids with azo compounds for synthesis of arylhydrazides. *Organic & biomolecular chemistry*, 14(28): 6821-6825.
- Liu L, Xi Z, 2018. Organocopper (III) Compounds with Well-defined Structures Undergo Reductive Elimination to Form C—C or C–Heteroatom Bonds. *Chinese Journal of Chemistry*, 36(12): 1213-1221.
- Nguyen MH, Smith III AB, 2013. Copper-catalyzed electrophilic amination of organolithiums mediated by recoverable siloxane transfer agents. *Organic letters*, 15(18): 4872-4875.
- Prakash GS, Gurung L, Marinez ER, Mathew T, Olah GA, 2016. Electrophilic amination of aromatics with sodium azide in BF₃–H₂O. *Tetrahedron Letters*, 57(3): 288-291.
- Shoji T, Sugiyama S, Takeuchi M, Ohta A, Sekiguchi R, Ito S, Yasunami M, 2019. Synthesis of 6-Amino- and 6-Arylazoazulenes via Nucleophilic Aromatic Substitution and Their Reactivity and Properties. *The Journal of organic chemistry*, 84(3): 1257-1275.
- Snieckus V, Kölmel DK, 2019. Buchwald–Hartwig Coupling of Piperidines with Hetaryl Bromides. *Synfacts*, 15(11): 1240.
- Ullmann F, 1903. *Ber Dtsch. On a new formation of diphenylamine derivatives.* [machine translation]. *Berichte der Deutschen Chemischen Gesellschaft*, (36): 2382-2384.
- Yoshikai N, Nakamura E, 2012. Mechanisms of nucleophilic organocopper (I) reactions. *Chemical reviews*, 112(4): 2339-2372.
- Wang N, Faber EB, Georg GI, 2019. Synthesis and spectral properties of 8-Anilino-naphthalene-1-sulfonic Acid (ANS) derivatives prepared by microwave-assisted copper (0)-catalyzed ullmann reaction. *ACS omega*, 4(19): 18472-18477.
- Watson SC, Eastham JF, 1967. Colored indicators for simple direct titration of magnesium and lithium reagents. *Journal of Organometallic Chemistry*, 9(1): 165-168.