# Versatile and base-free copper-catalyzed α-arylations of aromatic ketones using diaryliodonium salts

Maxime Bouquin, Florian Jaroschik, Marc Taillefer *

*ICGM, Univ Montpellier, CNRS, ENSCM, 34090 Montpellier, France*

## ARTICLE INFO

## ABSTRACT

A ligand and base-free copper catalyzed synthetic method for the efficient α-arylation of aromatic ketones is described. In order to avoid strong bases, ketone-derived silyl enol ethers were employed. Their reaction with diaryliodonium salts as aryl source provided the intermolecular C–C coupling displaying good functional group tolerance and requiring low catalyst loading.

© 2021 Elsevier Ltd. All rights reserved.

## Introduction

The α-arylation of aromatic ketones is a powerful synthetic tool in organic synthesis. As early as 1973, Semmelhack and co-workers reported a nickel catalyzed intramolecular α-arylation of lithium enolates as a fundamental step in the total synthesis of synthetic intermediates of cephalotaxinone [1]. Since then, α-arylation reactions have found many applications, for example, as the key step toward synthetic intermediates of active ingredients, such as Tamoxifen or Oxcarbazepine [2]. The most widely reported method to perform intermolecular α-arylations on aromatic ketones is the reaction of the corresponding enolate with aryl halides under palladium catalysis [3]. However, numerous other transition metal catalyzed or transition metal free α-arylations of enolizable aryl ketones have been disclosed [4]. Nevertheless, the high pKa of the α-proton of aromatic ketones (pKa = 25 in DMSO for acetophenone) [5], often requires the use of strong bases, complex ligands or harsh conditions, hence imposing certain limitations. In order to circumvent this issue, increased interest in the use of silyl enol ethers as starting compounds has emerged. Among the leading examples are the palladium or copper catalyzed stereoselective α-arylation reactions of esters, aliphatic ketones and imides silyl derivatives using aryl halides [6a], pseudo-halides [6b] or diaryliodonium sa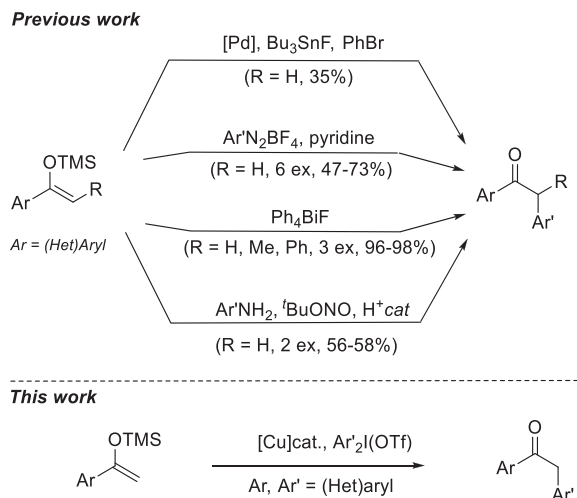lts as aryl source [7]. However, for arylketone derived enolsilanes, only few examples of α-arylation reactions exist in the literature [8–11].

Scheme 1 summarizes the several attempts using silyl enol ethers of aromatic ketones reported so far. The presented methodologies use toxic reagents, provide modest yields in most cases and have very limited scope. The earliest example was reported in 1982 by Uribe and co-worker [8]. They generated *in-situ* an organotin species and performed the α-arylation, using aryl bromides under palladium catalysis. However, the organotin species was generated by a stochiometric amount of toxic tin fluoride reagent and gave only one low-yield example for acetophenone with bromobenzene. Later, Tanaka and co-worker disclosed a transition metal free version of this reaction by using arene diazonium tetrafluoroborate [9]. This radical process is initiated by the interaction of the diazonium salt and pyridine, the latter acting as reagent and solvent. Maruoka et al. described in 2003 an efficient α-arylation of ketones with a tetraphenylfluorobismuth reagent [10]. Despite high yields with several enol substrates, the bismuth reagent had to be used in stochiometric amount, only one out of the four aryl groups was transferred, and the scope was limited to the phenyl group. In 2014, the Gonzalez-Gomez group described a Brønsted acid catalyzed system [11]. They generated *in-situ* a diazonium salt from anilines as the aryl source. However, this reaction required a huge excess of silyl enol ether and they reported only two examples from aromatic ketone derivatives.

Herein, we describe a ligand-free copper-catalyzed α-arylation of aryl ketones under their silyl enol ether form using diaryliodonium salts as aryl source [12].

---

\* Corresponding author.
  *E-mail address:* marc.taillefer@enscm.fr (M. Taillefer).

**Previous work**

Scheme 1 structures:

OTMS / Ar, R (Ar = (Het)Aryl)

[Pd], Bu₃SnF, PhBr
(R = H, 35%)

Ar'N₂BF₄, pyridine
(R = H, 6 ex, 47-73%)

Ph₄BiF
(R = H, Me, Ph, 3 ex, 96-98%)

Ar'NH₂, $^t$BuONO, H$^+$cat
(R = H, 2 ex, 56-58%)

→ Ar–C(O)–CH(R)(Ar')

**This work**

OTMS / Ar → [Cu]cat., Ar'₂I(OTf) → Ar–C(O)–CH₂–Ar'
Ar, Ar' = (Het)aryl

**Scheme 1.** α-Arylation using arylketone derived enolsilanes.

## Results & discussions

For our first trials, we chose the following readily available substrates: the silyl enol ether of acetophenone **1a** (3 equiv) and diphenyliodonium triflate **2a** (1 equiv). Using copper(II) acetate (10 mol%) as precatalyst, phenantroline (10 mol%) as additive and 1,2-dichloroethane (DCE) (0.5 M) as solvent, we obtained 52% of expected 2-phenylacetophenone **3aa** (Table 1, entry **1**) at 25 °C and 80% at 70 °C (entry **2**).

Ligand free conditions allowed the formation of **3aa** with similar yield (entry **3**), whatever the copper source, including Cu(OTf)₂, CuI or CuBr (see Supporting Information). The copper-free conditions gave traces of product and pointed out the crucial role of

the metal (entry **4**). Under aerobic conditions, the formation of **3aa** was observed but the process was less effective (entry **5**). The change of the counter anion of diphenyliodonium from triflate to hexafluorophosphate induced slightly lower yield (entry **6**), while reducing the reaction time from 16 h to 2 h did not decrease the formation of **3aa** (entry **7**). We then studied the copper loading which could be reduced to 0.5 mol% (entry **8–9**) without affecting the yield, whereas an even lower copper loading (0.25 mol%) gave only a fair 49% of **3aa** (entry **10**). Reducing the amount of **1a** from 3 to 1.5 equivalents, slightly decreased the yield (entry **11**). Surprisingly with this ratio, additional shortening of the reaction time to 0.5 h afforded **3aa** in 84% NMR yield and 80% isolated yield (entry **12**).
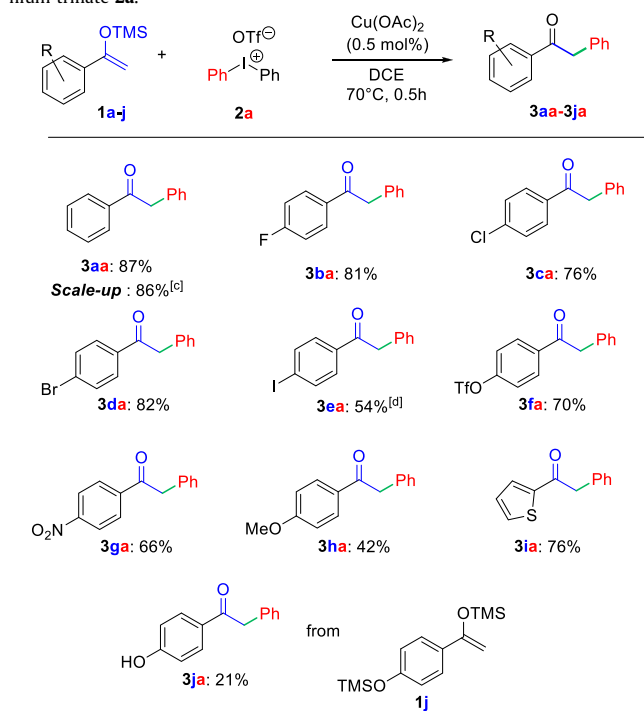
With these optimized conditions in hand, we explored the scope for α-arylation of silyl ether enol **1a** with different symmetrical diaryliodonium salts **2a–e** (Ar₂ = Ar₁, Table 2). Halogen groups on substrates **2b–c** (Cl and Br respectively) were found to be suitable and afforded the α-arylated product **3ab–ac** in good yields. Di (*p*-methylphenyl)iodonium triflate **2d** also led to the formation of the corresponding α-arylated product **3ad** in moderate yield.

Besides, we tested the mesitylaryliodonium salt strategy, in which the sterically hindered mesityl group would act as a dummy ligand and thus favor the addition of the other aryl group [13]. Consequently, mesitylaryliodonium salts **2a′–2d′** (Ar₂ = mesityl) were engaged to make a comparison with the corresponding symmetrical diaryliodonium salts and similar or slightly lower isolated yields were observed for **3aa–3ad** (Table 2). Interestingly, although symmetrical di(*p*-fluorophenyl) triflate did not afford the α-arylated product, mesityl(*p*-fluorophenyl)iodonium triflate **2e′** gave

**Table 1**
Copper catalyzed α-arylation of 1-phenyl-1-trimethylsilyloxyethylene **1a** with diphenyliodonium triflate **2a**: reaction conditions.[ab]

Reaction scheme:
OTMS (1a, x equiv) + Ph₂I⁺ OTf⁻ (2a, 1 equiv) → Cu(OAc)₂ (y mol%), DCE [0.5M], 25 to 70°C, 0.5 to 16h → PhC(O)CH₂Ph (3aa)

| Entry | **1a** (equiv) | [Cu] (mol%) | t (h) | Yields (%) |
|---|---|---|---|---|
| **1**[cd] | 3 | 10 | 16 | 52 |
| **2**[d] | 3 | 10 | 16 | 80 |
| **3** | 3 | 10 | 16 | 82 |
| **4** | 3 | 0 | 16 | 2 |
| **5**[e] | 3 | 10 | 16 | 60 |
| **6**[f] | 3 | 10 | 16 | 73 |
| **7** | 3 | 10 | 2 | 82 |
| **8** | 3 | 5 | 2 | 84 |
| **9** | 3 | 0.5 | 2 | 84 |
| **10** | 3 | 0.25 | 2 | 49 |
| **11** | 1.5 | 0.5 | 2 | 70 |
| **12** | 1.5 | 0.5 | 0.5 | 84 (80)[g] |

[a] Reaction conditions: **1a** (0.375–0.75 mmol), **2a** (0.25 mmol), Cu(OAc)₂ (0.0013–0.025 mmol) and 1,2-dichloroethane (DCE) (0.5 mL) for 0.5–16 h at 70 °C unless mention, under an argon atmosphere.
[b] NMR yields using trichloroethylene as an internal standard.
[c] Reaction performed at 25 °C.
[d] Reaction performed with phenantroline (10 mol%, 0.025 mmol).
[e] Reaction performed under air atmosphere.
[f] Reaction performed with hexafluorophosphate as counter anion.
[g] Isolated yield.

**Table 2**
Copper catalyzed α-arylation of 1-phenyl-1-trimethylsiloxyethylene **1a** and diaryliodonium triflates **2a–k**.[ab]

Reaction scheme:
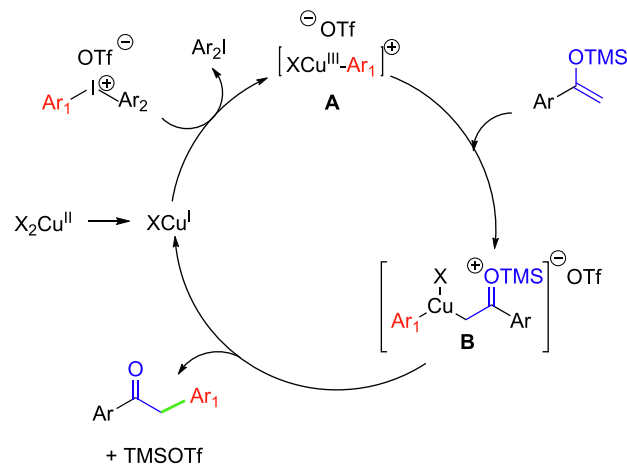OTMS/Ph (1a) + Ar₁–I⁺–Ar₂ OTf⁻ (2a-k) → Cu(OAc)₂ (0.5 mol%), DCE, 70°C, 0.5h → PhC(O)CH₂–Ar₁ (3aa-3ak)

**3aa**
Ar₂ = Ar₁ : 80%
Ar₂ = Mesityl : 79%[c]

**3ab** (Cl)
Ar₂ = Ar₁ : 82%
Ar₂ = Mesityl : 69%[c]

**3ac** (Br)
Ar₂ = Ar₁ : 77%
Ar₂ = Mesityl : 76%[c]

**3ad** (CH₃)
Ar₂ = Ar₁ : 56%
Ar₂ = Mesityl : 54%[c]

**3ae** (F)
Ar₂ = Ar₁ : 0%
Ar₂ = Mesityl : 70%[c]

**3af** (CH₃)
Ar₂ = Mesityl : 77%[c]

**3ag** (CH₃)
Ar₂ = Mesityl : 20%[c]

**3ah** (CF₃)
Ar₂ = Mesityl : 63%[c]

**3ai** (CO₂Et)
Ar₂ = Mesityl : 71%[c]

**3aj** (C(O)CH₃)
Ar₂ = Mesityl : 65%[c]

**3ak** (Ph)
Ar₂ = Mesityl : 84%[c]

[a] Reaction conditions: 1-phenyl-1-trimethylsiloxyethylene **1a** (0.375 mmol), diaryliodononium triflate (0.25 mmol, Ar₂ = Ar₁), Cu(OAc)₂ (0.00125 mmol), DCE (0.5 mL) at 70 °C during 0.5 h. [b] Isolated yield. [c] Reaction performed with 1-phenyl-1-trimethylsiloxyethylene **1a** (0,5 mmol) and mesitylaryliodonium triflate (0.25 mmol, Ar₂ = mesityl). Mesityl = 2,4,6-trimethylphenyl.

**Table 3**
Copper catalyzed α-arylation of several aryl silyl enol ethers **1a–j** and diphenyliodonium triflate **2a**.[ab]



[a]Reaction conditions: aryl silyl enol ether (0.625 mmol), diphenyliodonium triflate 2a (0.25 mmol), Cu(OAc)$_2$ (0.00125 mmol), DCE (0.5 mL) at 70 °C during 0.5 h. [b]Isolated yield. [c]Reaction performed with 2.5 mmol scale. [d]Reaction performed with 0.375 mmol of aryl silyl enol ether.



**Scheme 2.** Mechanism proposal.

**3ae** in good yield. We continued the aryl scope with mesitylaryliodonium salts **2f–k**. It is noteworthy that *m*- or *o*-methyl substituted mesitylaryliodonium salts **2f–2g** were compatible, affording **3af–3ag** in good and low yields, respectively, probably due to steric hindrance. Mesitylaryliodonium salts bearing an electron withdrawing (EWG) group, such as trifluoromethyl **2h**, ethyl ester **2i** or ketone **2j** were applied forming **3ah–3aj** in moderate to good yields. A biphenyl group on mesitylaryliodonium **2k** was suitable and gave **3ak** in good yield. However, bulky aryls (mesityl and 1-napthyl) or pyridyl groups on the mesitylaryliodonium salts were not tolerated in our conditions (see Supporting Information).

The scope of this α-arylation procedure was further explored with several functionalized aryl silyl enol ethers **1a–j** and diphenyliodonium triflate **2a** as aryl source (see Table 3). Halogens on silyl ether enol **1b–1e**, notably iodine, were well tolerated and gave the corresponding products **3ba–3ea** in good yields. In the same way, the silyl enol ether with a triflate group **1f** was successfully engaged in this α-arylation process, affording the corresponding product **3fa** without any degradation. To the best of our knowledge, this is the first reported α-arylation process tolerating the triflate group as a functional group on the ketone. Electron withdrawing groups on silyl enol ether such as the nitro-substituted **1g** induced a slight drop of the yield and gave **3ga** in 66% yield. However, electron donating groups, such as the *p*-methoxy substituted substrate **1h**, showed limited reactivity and afforded product **3ha** in moderate yield. Heteroaromatic silyl enol ether **1i**, bearing a thienyl group was employed and allowed the formation of **3ia** in good yield. Pyridyl groups were again not suitable (see Supporting Information). We then tried a temporary protecting strategy in order to assess the tolerance with nucleophilic functional groups such as a hydroxyl one. From the OTMS protected

precursor **1j**, we obtained, after work-up, the corresponding deprotected α-arylated product **3ja** in low yield without arylation of the nucleophilic functional group. Note that the reaction also proved to be suitable for scale-up experimentation (2.5 mmol), delivering the product **3aa** in excellent yield (Table 3).

Concerning the mechanism of the reaction, at this stage, we believe that a radical-type reaction is unlikely due to the good tolerance towards halogen substrates, including iodide. In accordance with previous reports in the literature [14], a plausible intermediate for this system involves a Cu(III) species **A** resulting from the oxidative addition of Cu(I) into the Ar-I bond of the diaryliodonium salt (Scheme 2). This key intermediate **A** could then react with silyl enol ether to give the mixed copper(III)arylalkyl complex **B**. The latter would undergo a reductive elimination to regenerate the Cu(I) catalytic species and to yield the expected α-arylated ketone after the removal of the silyl group with the triflate anion.

## Conclusion

In summary, we have reported an efficient copper-catalyzed α-arylation of aromatic ketones under their silyl enol ether form using symmetrical diaryliodonium or mesitylaryliodonium salts as aryl source. This ligand and base-free process showed good tolerance toward sensitive functional groups such as triflate or iodine. Work is in progress to broaden further the scope of this catalytic system and to study the mechanism.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153208.

# References

[1] M.F. Semmelhack, R.D. Stauffer, T.D. Rogerson, Tetrahedron Lett. 14 (1973) 4519–4522.

[2] a) G. Danoun, A. Tlili, F. Monnier, M. Taillefer, Angew. Chem. Int. Ed. 51 (51) (2012) 12815–12819;
b) M.P. Drapeau, I. Fabre, L. Grimaud, I. Ciofini, T. Ollevier, M. Taillefer, Angew. Chem. Int. Ed. 54 (36) (2015) 10587–10591;
c) M. Carril, R. SanMartin, F. Churruca, I. Tellitu, E. Dominguez, Org. Lett. 7 (22) (2005) 4787–4789.

[3] a) M. Palucki, S.L. Buchwald, J. Am. Chem. Soc. 119 (1997) 11108–11109;
b) B.C. Hamman, J.F. Hartwig, J. Am. Chem. Soc. 119 (1997) 12382–12383;
c) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, Angew. Chem. Int. Ed. Engl. 36 (1997) 1740–1742.

[4] a) Selected reviews: C.C.C. Johansson, T. Colacot Angew. Chem. Int. Ed. 49 (2010) 676–707;
b) F. Bellina, R. Rossi, Chem. Rev. 110 (2) (2010) 1082–1146;
c) , Selected recent examples:S. Ge, J.F. Hartwig J. Am. Chem. Soc. 133 (41) (2011) 16330–16333;
d) G. Danoun, A. Tlili, F. Monnier, M. Taillefer, Angew. Chem. Int. Ed. 51 (51) (2012) 12815–12819;
e) Q.-L. Xu, H. Gao, M. Yousufuddin, D.H. Ess, L. Kürti, J. Am. Chem. Soc. 135 (38) (2013) 14048–14051;
f) S. Ge, W. Chaladaj, J.F. Hartwig, J. Am. Chem. Soc. 136 (11) (2014) 4149–4152;
g) R. Takise, K. Muto, J. Yamaguchi, K. Itami, Angew. Chem. Int. Ed. 52 (26) (2014) 6791–6794;
h) J.A. Fernandez-Salas, E. Marelli, D.B. Cordes, A.M.Z. Slawin, S.P. Nolan, Angew. Chem. Int. Ed. 21 (10) (2015) 3906–3909;
i) W.C. Fu, C.M. So, O.Y. Yuen, I.T.C. Lee, F.Y. Kwong, Org. Lett. 18 (8) (2016) 1872–1875;
j) T. Chen, Y.-F. Li, Y. An, F.-M. Zhang, Org. Lett. 18 (18) (2016) 4753–4757;
k) E. Marelli, Y. Renault, S.V. Sharma, S.P. Nolan, R.J.M. Goss, Angew. Chem. Int. Ed. 23 (16) (2017) 3832–3836;
l) I. Astarloa, R. SanMartin, M.T. Herrero, E. Dominguez, Adv. Synth. Catal. 360 (8) (2018) 1711–1718;
m) X. Rao, N. Li, H. Bai, Z. Whang, W. Tang, Angew. Chem. Int. Ed. 57 (38) (2018) 12328–12332;
n) X. Chen, Z. Chen, C.M. So, J. Org. Chem. 84, 10 (2019) 633è-6346;
o) X.-X. Nie, Y.-H. Huang, P. Wang, Org. Lett. 22 (19) (2020) 7716–7720;
p) Z. Li, Y. Peng, T. Wu, Org. Lett. 23 (3) (2021) 881–885;
q) N.V. Kolotilo, A.A. Sinitsa, Yu.V. Rassukana, P.P. Onys'ko, Zh. Obshch. Khim. 76 (2006) 1260, Chem. Abstr. **2006**, 146, 316980.

[5] F.G. Bordwell, M. Van der Puy, N.R. Vanier, J. Org. Chem. 41 (10) (1976) 1883–1885.

[6] a) X. Liu, J.F. Hartwig, J. Am. Chem. Soc. 126 (16) (2004) 5182–5191;
b) Z. Huang, Z. Liu, J.S. Zhou, J. Am. Chem. Soc. 133 (40) (2011) 15882–15885.

[7] a) J.S. Harvey, S.P. Simonovich, C.R. Jamison, D.W.C. MacMillan, J. Am. Chem. Soc. 133 (35) (2011) 13782–13785;
b) A. Bigot, A.E. Williamson, M.J. Gaunt, J. Am. Chem. Soc. 133 (35) (2011) 13778–13781.

[8] I. Kuwajima, H. Urabe, J. Am. Chem. Soc. 104 (24) (1982) 6831–6833.

[9] T. Sakakura, M. Hara, M. Tanaka, J. Chem. Soc., Perkin Trans 1 (1994) 283–288.

[10] T. Ooi, R. Goto, K. Maruoka, J. Am. Chem. Soc. 125 (35) (2003) 10494–10495.

[11] D. Felipe-Blanco, J.C. Gonzalez-Gomez, Adv. Synth. Catal. 14 (360) (2018) 2773–2778.

[12] M. Escudero-Casao, G. Licini, M. Orlandi, During the preparation of this manuscript, Orlandi and co-workers disclosed an enantioselective copper-catalyzed α-arylation of TMS-enol ethers of ketones in combination with mesitylaryliodonium salts, J. Am. Chem. Soc. 143 (9) (2021) 3289–3294.

[13] N.R. Deprez, M.S. Sanford, Inorg. Chem. 46 (6) (2007) 1924–1935.

[14] a) For recent or significant examples: T.P. Lockhart J. Am. Chem. Soc. 105 (7) (1983) 1940–1946;
b) R.J. Phipps, N.P. Grimster, M.J. Gaunt, J. Am. Chem. Soc. 130 (26) (2008) 8172–8174;
c) R.J. Phipps, M.J. Gaunt, Science 323 (5921) (2009) 1593–1597;
d) R.J. Phipps, L. McMurray, S. Ritter, H.A. Duong, M.J. Gaunt, J. Am. Chem. Soc. 134 (26) (2012) 10773–10776;
e) S. Zhu, D.W.C. MacMillan, J. Am. Chem. Soc. 134 (26) (2012) 10815–10818;
f) N. Gigant, L. Chausset-Boissarie, M.-C. Belhomme, T. Poisson, X. Pannecouke, I. Gillaizeau, Org. Lett. 15 (2) (2013) 278–281;
g) M.V. Ivanova, A. Bayle, T. Besset, T. Poisson, X. Pannecoucke, Angew. Chem. Int. Ed. 54 (45) (2015) 13406–13410;
h) J. Li, H. Wang, Y. Hou, W. Yu, S. Xu, Y. Zhang, Eur. J. Org. Chem. 14 (2016) 2388–2392;
i) A. Sinai, A. Mészaros, T. Gati, V. Kudar, A. Pallo, Z. Novak, Org. Lett. 15 (23) (2013) 5654–5657;
j) A. Sinai, D. Vangel, T. Gati, P. Bombicz, Z. Novak, Org. Lett. 17 (2015) 4136–4139;
k) K. Aradi, Z. Novak, Adv. Synt Catal 357 (2015) 371–376;
l) A. Székely, A. Sinai, E.D. Toth, Z. Novak, Synthesis 14 (2014) 1871–1880;
m) K. Aradi, P. Bombicz, Z. Novak, J. Org. Chem. 81 (2016) 920–931;
n) K. Aradi, A. Mészaros, B.L. Toth, Z. Vincze, Z. Novak, J. Org. Chem. 82 (2017) 11752–11764;
o) T.K. Stenczel, A. Sinai, Z. Novak, A. Stirling, Beilstein J. Org. Chem. 14 (2018) 1743–1749.