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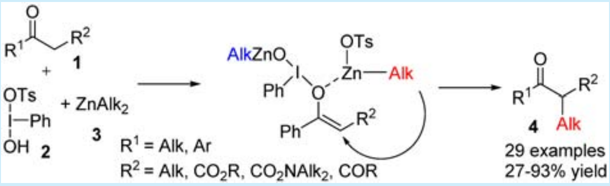
Oxidative Umpolung α-Alkylation of Ketones

O. Svetlana Shneider,[†] Evgeni Pisarevsky,[†] Peter Fristrup,[‡] and Alex M. Szpilman*[,†]

[†]Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, 3200008, Haifa, Israel
[‡]Department of Chemistry, Technical University of Denmark, DK-2800, Kgs. Lyngby, Denmark

Ⓢ *Supporting Information*

ABSTRACT: We disclose a hypervalent iodine mediated α-alkylative umpolung reaction of carbonyl compounds with dialkylzinc as the alkyl source. The reaction is applicable to all common classes of ketones including 1,3-dicarbonyl compounds and regular ketones via their lithium enolates. The α-alkylated carbonyl products are formed in up to 93% yield. An ionic mechanism is inferred based on meticulous analysis, NMR studies, trapping and crossover experiments, and computational studies.

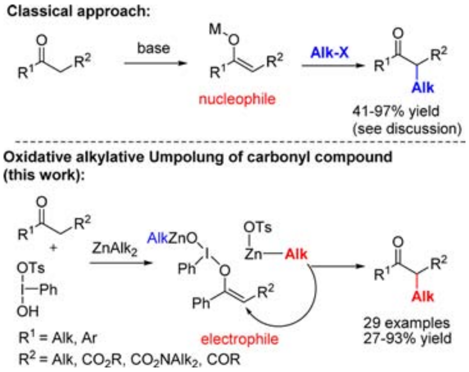


Umpolung reactions represent an invaluable tool for molecular assembly,[1] providing flexibility, chemoselectivity, and sometimes enhanced reactivity. An illustration of the power of the umpolung concept is its application in total synthesis.[2] Because umpolung reactivity is anomalous to classical chemistry by definition, the development of umpolung chemistry entails exploration of unchartered chemical reactivity space and, consequently, new discoveries in this area are rare. Indeed, the inherent difficulty of achieving polarity reversal means that umpolung is commonly accomplished by heteroatom substitution in multistep protocols, such as the classical thioacetal umpolung of aldehydes.[1,3,4]

A powerful way of achieving direct umpolung in a single step is through the use of hypervalent iodine reagents.[5] However, hypervalent iodine mediated C−C bond forming reactions are limited to introduction of aryl (sp^2),[6,7] alkenyl (sp^2),[8] and alkynyl (sp)[9] at carbonyl α-positions.[5] In contrast, only perfluorinated alkyl (sp^3) substituents can be introduced through this reactivity manifold.[10] This may be due to the instability of alkyl iodide(III) compounds.[5] All of these reactions use the carbonyl compound in the classical sense as a nucleophile, and it is the alkenyl, alkynyl, or aryl moiety that is polarity reversed by the hypervalent iodine (Scheme 1). The reverse approach, i.e., umpolung of the carbonyl α-position by hypervalent iodine reagents, has been used successfully for the introduction of various heteroatoms including halogen, oxygen, and nitrogen.[5] The only example of C−C bond formation is the iodosylbenzene/HBF_4 mediated allylation of silyl enolethers reported by Calpe and Zefirov[11] and enol dimerization.[5] C−C bond formation using alkyl-metal species has so far not been reported. Yet such a direct single step oxidative alkylation of carbonyl compounds would significantly expand the scope of umpolung strategies.[4,12]

In this paper, we disclose the oxidative umpolung α-alkylation of carbonyl compounds by Koser's reagent and dialkylzinc reagents (Scheme 1). We also report preliminary mechanistic studies that show that the reaction takes place via hypervalent iodine mediated oxidative umpolung of the ketone.

Scheme 1. Conceptual Differences between Classical and Umpolung Alkylation (This Work)



We envisioned achieving umpolung of the ketone enolate into an α-electrophile by the action of a two-electron hypervalent iodine oxidant ($PhIX_2$) and subsequent addition of an alkyl nucleophile. Several challenges presented themselves for the intended transformation. For example, the carbonyl compound could undergo oxidative dimerization[13,5d] or α-functionalization by attack of other reactive nucleophiles present or formed in the course of the reaction.[5] In addition, the "normal" 1,2-addition of alkyl-metal reagents to the carbonyl group prior to the oxidative step had to be precluded. These considerations led us to focus on trialkyl aluminum and dialkyl zinc reagents.

We chose β-keto ester **1** (Table 1) as our model substrate since it has a high enol content in toluene and a low tendency to undergo α-heteroatom substitution and was of synthetic interest, as we would be forging a difficult to form quaternary carbon center in the reaction. Experiments with oxidants **3−8** (Figure 1) led to recovery of unreacted β-keto-ester **1** (see Table S1, entries 1−6). In contrast, reaction of the more reactive **10** with Koser's

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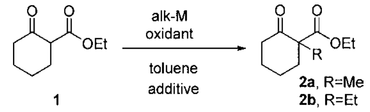
Table 1. Optimization of the Reaction[a]



entry	oxidant	alk-M	additive	t/°C	product	yield (cons.)/%
1	**9**	Me_3Al	none	-78	**2a**	18 (18)
2	**9**	Me_3Al	$MgSO_4$	-78	**2a**	49 (100)
3	**9**	Me_3Al	4ÅMS	-78	**2a**	47 (100)
4	**9**	Me_2Zn	$MgSO_4$	-78	**2a**	80 (100)
5	**9**	Et_2Zn	$MgSO_4$	-78	**2b**	28 (100)
6	**9**	Et_2Zn	$MgSO_4$/ethanolamine[b]	-78	**2b**	50 (100)

[a] 2 equiv of organometal and oxidant. [b] 1 equiv.

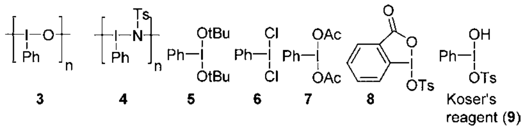
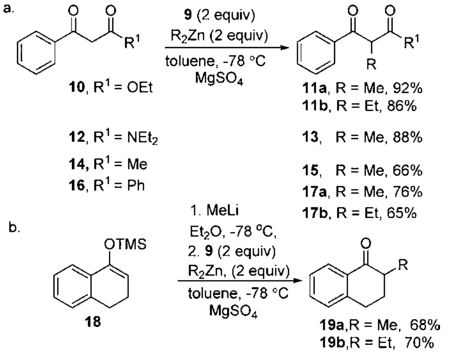


Figure 1. Oxidants screened during optimization of the reaction.

reagent (**9**) led to formation of a tosylated product in 80% yield (see Supporting Information (SI) and Scheme 2a for the structure of **10**).[14] It is well-known that Koser's reagent tosylates β-keto esters rapidly at ambient temperature.[15] We found that the tosylation reaction could be effectively suppressed when the reaction was performed below 0 °C. When the reaction of **1** with trimethylaluminum (2 equiv) and Koser's reagent (**9**) (2 equiv) was carried out at −78 °C in toluene, product **2a** (R = Me) was isolated in 18% yield along with 82% recovered starting material (Table 1, entry 1). Coordinating solvents inhibit the reaction. By screening numerous additives, we found that, in the presence of the desiccant magnesium sulfate, quantitative consumption of the starting material occurred, affording **2a** (R = Me) in 49% isolated yield (entry 2). No other products were observed by TLC. The use of molecular sieves led to formation of **2a** in 47% isolated yield (entry 3). Switching to dimethylzinc increased the isolated yield of the alkylated product **2a** (R = Me) to 80% (entry 4). The order of addition reagents is inconsequential for the yield and progress of the reaction. The reaction of **1** with diethylzinc afforded the product **2b** (R = Et) in 28% yield (entry 5). It is well-known that the reactivity of dialkylzinc can be increased by the addition of amino alcohols.[16] When ethanolamine (1 equiv) was added to the reaction, the ethylated product **2b** was isolated in 50% yield (entry 6). Other aminoalcohols proved inferior to ethanolamine. For comparison **2a** and **2b** have been prepared in 97% and 55% yield respectively using the classical conditions of base, alkyl iodide and heat.[17]

To demonstrate the potential of the umpolung alkylation reaction, we applied it to a broad range of ketones (Scheme 2). For example, β-keto ester **10** reacted under the standard conditions to give only the monoalkylated product **11a** in 92% yield (Scheme 2a). Ethylation in the presence of ethanolamine proceeded to give **11b** in 86% yield. Reaction of β-keto amide (**12**) led to formation of **13** in 88% yield (Scheme 2a). Both alkyl substituted 1,3-diketone **14** and aryl substituted diketone **16** (Scheme 2a) gave the alkylated products in 66% (**15**), 76% (**17a**), and 65% (**17b**) yields, respectively. For comparison **10** has been ethylated under classical conditions using NaH and ethyl bromide in DMF at 60 °C to afford **11b** in 45% yield.[18] Synthesis of **17b** from **16** using excess ethyl iodide and TBAF at rt overnight proceeds in 41% yield.[19]

Scheme 2. Scope of Reaction for 1,3 Bis Carbonyl Substrates (a) and Simple Ketones (b)



10, R^1 = OEt → **11a**, R = Me, 92%; **11b**, R = Et, 86%

12, R^1 = NEt_2 → **13**, R = Me, 88%

14, R^1 = Me → **15**, R = Me, 66%

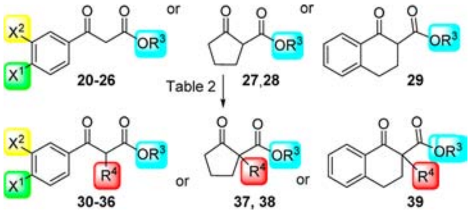
16, R^1 = Ph → **17a**, R = Me, 76%; **17b**, R = Et, 65%

18 → **19a**, R = Me, 68%; **19b**, R = Et, 70%

Importantly, the lithium enolate, prepared from the TMS enolether **18** of tetralone by the action of MeLi, reacted with Koser's reagent **9** and dimethyl or diethylzinc to form alkylated ketones **19a** and **19b** in 68% and 70% yield, respectively (Scheme 2b). The lithium enolate could also be prepared by the reaction of tetralone using LDA. Subsequent reaction of the enolate with Koser's reagent and diethylzinc afforded **19b** in 50% yield. For comparison, alkylation of tetralone using LDA and ethyl bromide, methyl iodide, or ethyl iodide proceeds in 41−65% yield.[20]

These results show that the reaction has the potential to be a strategically important umpolung alternative to classical alkylation chemistry for a broad range of carbonyl compounds. Significantly, while dialkylation is a common problem under

Table 2. Study of Functional Group Tolerance[a]



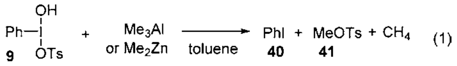
entry	product	proc.	X^1	X^2	R^3	R^4	yield
1	**30a**	A	Me	H	Et	Me	87%
2	**30b**	B	Me	H	Et	Et	85%
3	**30c**	B	Me	H	Et	Bu	54%
4	**31a**	A	F	H	Et	Me	82%
5	**31b**	B	F	H	Et	Et	85%
6	**32**	A	Cl	H	Et	Me	80%
7	**33a**	A	NO_2	H	Et	Me	92%
8	**33b**	B	NO_2	H	Et	Et	33%
9	**34a**	A	OMe	OMe	Et	Me	90%
10	**34b**	B	OMe	OMe	Et	Et	61%
11	**35a**	A	H	H	allyl	Me	92%
12	**35b**	B	H	H	allyl	Et	93%
13	**36**	A	H	H	propargyl	Me	93%
14	**37a**	A	–	–	Et	Me	82%
15	**37b**	B	–	–	Et	Et	74%
16	**38**	A	–	–	cholesteryl	Me	80%
18	**39a**	A	–	–	Et	Me	93%
19	**39b**	B	–	–	Et	Et	27%

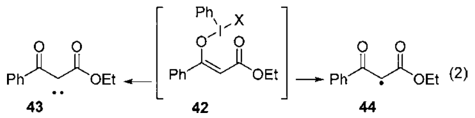
[a] Procedure A: **9** (2 equiv), Me_2Zn (2 equiv), $MgSO_4$, toluene −78 °C. Procedure B: same as A but with **9** (4 equiv), Et_2Zn (4 equiv).

classical conditions, in all of these experiments (Scheme 2), only monoalkylated products were observed.

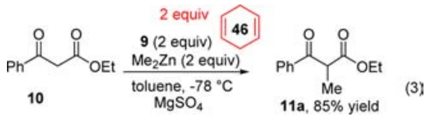
We evaluated the functional group tolerance of the reaction for a number of functionalized β-keto esters (Table 2). The reaction is compatible with a wide range of alkyl-substituted and aryl-substituted substrates. Functionalities such as fluoro, chloro, nitro, and methoxy aryl substituents are tolerated (products **31**, **32**, **33**, and **34**, entries 4−10). The reaction is compatible with alkene and alkyne functionalities as shown by the formation of products **35**, **36**, and **38** (Table 2, entries 11−13 and 16).

To provide insight into this novel transformation, we embarked on a mechanistic study. A careful product analysis showed that in addition to the desired product, and iodobenzene **40**, alkyl tosylates e.g. **41** were also formed (eq 1). Additionally, gas evolution (methane or ethane) was observed. Methyl tosylate was shown to be the product of the reaction of Koser's reagent **11** with trimethylaluminum or dimethylzinc in the absence of carbonyl compounds (eq 1). This side reaction leads to loss of the reactive reagent in a time dependent manner. Alkyl tosylates acting as alkylating agents in the reaction were unambiguously ruled out by carrying out the umpolung alkylation of **10** in the presence of d_3-methyl tosylate d_3-**41**.[14] Product **11a** was isolated in 93% yield with no detectable trace of d_3-methylated product.[14]



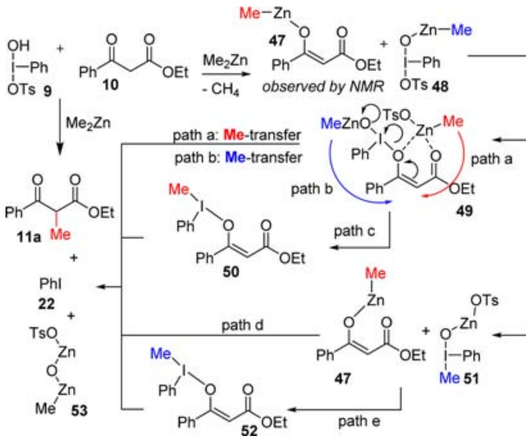


We surmised that the reaction might proceed via a C-[21] or O-bound[7] I(III) enolate such as **42** (eq 2). This enolate could react via a carbene, radical, or ionic pathway.[5] A carbene, e.g. **43**, can be generated from α-methylene-1,3-bis-carbonyl compounds via formation of formal C═I iodide(III) species.[5,22] However, since the present reaction proceeds for alkyl-substituted compounds such as **1**, a carbene intermediate is precluded. Iodide(III) enolate **42** may break down homolytically to give a C-centered radical i.e. **44**. To detect a possible radical intermediate, the reaction of β-keto ester **10** was carried out in the presence of C_{60} (**45**), an effective radical trapping agent (see Scheme S1).[23] GC-HRMS analysis of the reaction mixture showed no trace of C_{60}-**10** adducts.[14] Only trace amounts of ethylated C_{60} **46** could be detected by HRMS. The major C_{60} component in the reaction mixture was unreacted C_{60}. The formation of ethyl radicals from diethylzinc by the action of oxygen has been described by Feringa.[24] The possibility of an alkyl-radical or radical **44** participating in product formation was additionally ruled out by carrying out the reaction of **10** with dimethylzinc in the presence of 2 equiv of the powerful hydrogen atom donor, 1,4-cyclohexadiene (**29**) (eq 3). This experiment led to formation of **11a** in 85% yield indicating that a radical mechanism is unlikely.



The remaining alternative was an ionic mechanism. We identified five distinct possible mechanistic pathways (paths a−e, Scheme 3). Paths a and c would be distinguishable from paths b, d, and e only by the source of the transferred alkyl group. As shown in Scheme 3, **10** reacts with dialkylzinc to give the NMR observable O-bound zinc enolate **47** with evolution of methane gas.[14,25] Analogously, reaction of Koser's reagent (**9**) with dimethylzinc leads to methane evolution consistent with the formation of the corresponding zinc alkoxide **48**.

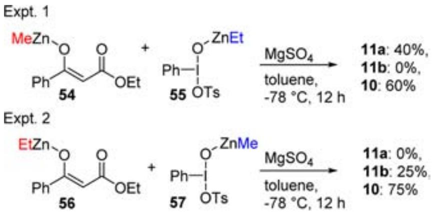
Scheme 3. Mechanisms a−e



These two species may combine through nucleophilic substitution of OTS on **48** by **47** to form **49**. Direct methyl transfer may take place from MeZnOTs (red methyl, path a) or from the MeZnO bound to I(III) (blue methyl path b) to give **11a**. In path c transfer of methyl to I(III) would lead to formation of **50** and a reductive elimination-like step lead to products. In paths d and e rearrangement of **48** would occur to form an unstable[5,26] hypervalent alkyl iodide(III) species **51** which could act as a classical electrophile and alkylate **47** (path d). Alternatively, nucleophilic attack by **47** on the iodine atom of **51** would lead to formation of **52**. Iodine(III) enolate **52** differs from **50** only by the source of the methyl group. I(III) enolate **52** would then undergo a reductive elimination-like step to give the observed products.

To distinguish between these disparate possibilities, we carried out a crossover experiment (Scheme 4). We formed the methyl-zinc-enolate **54** by the reaction of *dimethylzinc* and β-keto-ester **10**. In a separate vessel, Koser's reagent (**9**) was reacted with *diethylzinc* to give **55**. In both vessels, gas evolution could be clearly observed. The vessels were left at −78 °C for 8 h, then the content of the flask containing **55** was added to the vessel containing the enolate **54**, and the mixture was stirred for 12 h. After workup, the formation of a single alkylated product, namely **11a**, was observed in 40% yield, along with 60% unreacted starting material **10** (Experiment 1, Scheme 4). None of the alternative ethyl product **11b** could be detected. To rule out the possibility of a kinetic effect, the experiment was repeated, switching zinc reagents. In this experiment (Experiment 2,

Scheme 4. Crossover Experiments Rule out Paths b, d, and e



Scheme 4), the ethylated product **11b** was isolated in 25% yield along with 75% starting material. None of the methylated product (**11a**) was formed. These experiments show that alkyl transfer takes place from the alkylzinc originally bound in enolate **47** only and therefore unambiguously rule out paths b, d, and e.

A focused DFT-based computational study of the reaction was carried out to further elucidate the mechanism. Specifically, we were interested in whether the proposed mixed phenyl-methyl-iodine(III) **50** (Scheme 3, path c) would be able to selectively transfer the methyl group or if the proposed path c instead would result in formation of the phenyl-substituted product. Based on earlier computational studies,[7,27] we constructed a model system, consisting of a mixed alkyl-aryl iodine(III) enolate **50** (see SI Scheme S2).

The energy of the transition state for methyl transfer was 20 kJ/mol higher than the transition state for transfer of the phenyl moiety, calculated as the difference in Gibbs free energies at 195 K (−78 °C). Employment of implicit solvation (PB-SCRF, benzene) resulted in a marginally larger energy difference (23 kJ/mol). As only methyl transfer is observed in the reaction, these results rule out path c, leaving path a as the only plausible alternative.

We have designed, developed, and studied a hypervalent iodine mediated alkylative umpolung reaction of ketones. This reaction constitutes a strategic alternative to classical alkylation and an important addition to the umpolung arsenal. Experimental and computational evidence supports the reaction proceeding through an ionic mechanism (Scheme 3, path a). Importantly, it is applicable to a wide range of carbonyl compounds including normal ketones via their lithium enolates and 1,3-dicarbonyl compounds. Quaternary C-centers may be formed at low temperatures and mild conditions. Further studies including in asymmetric synthesis are underway in our laboratory.

■ ASSOCIATED CONTENT

S Supporting Information

Additional schemes, procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Szpilman@tx.technion.ac.il.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (b) Miyata, O.; Miyoshi, T.; Ueda, M. *ARKIVOC* **2013**, 60.

(2) (a) For a review, see: Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. For some selected examples, see: (b) Chen, M. Z.; Gutierrez, O.; Smith, A. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 1279. (c) Lee, K.; Kim, H.; Hong, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5735.

(3) For organocatalytic formation of acyl anion equivalents, see: (a) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (b) Rovis, T.; Nolan, S. P. *Synlett* **2013**, *24*, 1188.

(4) For an elegant three-step one-pot procedure for α-arylation and alkylation of ketones involving enamine formation using isoxazolidine (2 equiv) and alkylation with an organoaluminium reagent (2 equiv), see: Miyoshi, T.; Miyakawa, T.; Ueda, A.; Miyata, O. *Angew. Chem.* **2011**, *123*, 958.

(5) (a) Zhdankin, V. V.*Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*; Wiley: 2014. (b) Singh, F. V.; Wirth, T. Oxidative Functionalization with Hypervalent Halides. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford; 2014; Vol. 7, p 880. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (d) For a recent example of TMS-enolether dimerization, C−O and C−N bond formation through umpolung, see: Mizar, P.; Wirth, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 5993.

(6) Recent examples: (a) Allen, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (b) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782.

(7) Norrby, P.-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B. *Chem.—Eur. J.* **2010**, *16*, 8251.

(8) Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 9090.

(9) (a) Fernández González, D.; Brand, J. P.; Waser, J. *Chem.—Eur. J.* **2010**, *16*, 9457. (b) Fernández González, D.; Brand, J. P.; Mondière, R.; Waser, J. *Adv. Synth. Catal.* **2013**, *355*, 163.

(10) (a) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (b) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (d) Umemoto, T.; Gotoh, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 38. (e) Umemoto, T.; Kuriu, Y.; Nakayama, S. *Tetrahedron Lett.* **1982**, *23*, 1169.

(11) (a) Zhdankin, V. V.; Mullikin, M.; Tykwinski, R.; Berglund, B.; Caple, R.; Zefirov, N. S.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2605.

(12) For a radical organocatalytic allylation of ketones induced by cerium, see: Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20648.

(13) For a review, see: (a) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. For an example, see: (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.

(14) See Supporting Information for details.

(15) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487. For a review on Koser's reagent, see: Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365.

(16) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(17) (a) Winfield, C. J.; Al-Mahrizy, Z.; Gravestock, M.; Bugg, T. D. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3277. (b) Garvey, D. S.; Larosa, G. J.; Greenwood, J. R.; Frye, L. L.; Quach, T.; Cote, J. B.; Berman, J. WO2013058809A1, 2013.

(18) He, Z.; Li, H.; Li, Z. *J. Org. Chem.* **2010**, *75*, 4636.

(19) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934.

(20) (a) Adamczyk, M.; Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, *49*, 4226. (b) Eames, J.; Weerasooriya, N.; Coumbarides, G. S. *Eur. J. Org. Chem.* **2002**, 181. (c) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306.

(21) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.

(22) Neilands, O.; Karele, B. *Zh. Org. Khim.* **1965**, *1*, 1854. (b) Neilands, O.; Karele, B. *Zh. Org. Khim* **1966**, *2*, 488.

(23) Tzirakis, M. D.; Orfanopoulos, M. *Chem. Rev.* **2013**, *113*, 5262.

(24) (a) van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593. (b) Fernández-Ibáñez, M. Á.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2008**, *10*, 4041.

(25) (a) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1990**, *390*, C21. (b) Bolm, C.; Müller, J.; Zehnder, M.; Neuburger, M. A. *Chem.—Eur. J.* **1995**, *1*, 212.

(26) Guo, W.; Vallcorba, O.; Vallribera, A.; Shafir, A.; Pleixats, R.; Rius, J. *ChemCatChem* **2014**, *6*, 468.

(27) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem.—Eur. J.* **2013**, *19*, 10334.