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A Radical Bidirectional Fragment Coupling Route to Unsymmetrical Ketones

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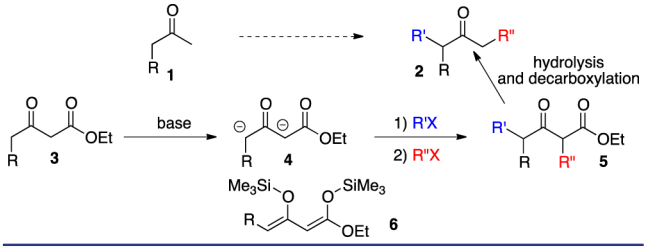
Supporting Information

ABSTRACT: A powerful strategy for the regioselective bidirectional synthesis of unsymmetrically substituted ketones is described, relying on the fact that the exchange of a xanthate is much faster than the radical addition to an unactivated alkene. The use of an alkene as the formal "alkylating" agent associated with the tolerance for numerous functional groups and the mildness of the experimental conditions removes many of the problems associated with the classical ionic and transition-metal-based approaches.

The alkylation of ketones is one of the fundamental reactions that is encountered early in the curriculum of undergraduate students, yet it is not one of the easiest to accomplish in practice. Complications arising from competing O-alkylation, formation of regioisomers, overalkylation as well as unwanted condensation reactions are very common.[1] The alternative use of primary alcohols as formal alkylating agents has recently been accomplished by certain transition-metal complexes through what is termed as redox catalysis.[2] In this approach, the alcohol is oxidized to the aldehyde, which then condenses with the ketone, and the resulting enone is finally reduced to the saturated ketone. The whole redox sequence takes place around the same metal. However, while this approach is attractive in terms of atom economy, it is still limited to simple structures and to ketone substrates, such as aryl alkyl ketones, that are not subject to problems of regiochemistry. A more general remedy for difficulties encountered in alkylating ketones involves the use of hydrazones, as first described by Corey and Enders and further refined and expanded by Enders et al. in studies spanning nearly four decades.[3]

The situation becomes more complex when a distal dialkylation of a ketone is contemplated, such as the transformation of ketone **1** into the higher unsymmetrical ketone **2** (Scheme 1).

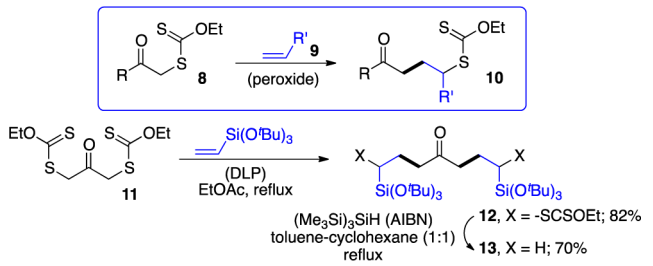
Scheme 1. Synthesis of Unsymmetrical Ketones



One solution, which has been mostly applied to the parent derivative (R = H), is to introduce a temporary electron-withdrawing group such as an ester (as in **3**), in order to cleanly differentiate the acidity of the protons on both sides of the ketone. Regioselective alkylation of the dianion **4** on the more reactive, generally less acidic site (Hauser's rule) followed by a second alkylation on the more acidic site gives dialkylated product **5**.[4] The auxiliary group is then removed by hydrolysis and decarboxylation in the case of ketoesters. Instead of dianions, the dienol silylethers **6** could in principle be used. These dienol silylethers have mostly been engaged in Mukaiyama-type aldol and Michael additions, but rarely in alkylation reactions.[5] In one recent disclosure, the regioselective palladium-catalyzed arylation of dienolsilylethers could be accomplished, but its extension to alkylation may not prove easy to implement.[5b] Various approaches to unsymmetrical ketones by fragment coupling have also been described, but these do not correspond to the equivalent of enolate alkylations.[6] Perhaps the most versatile in this respect is the umpolung strategy based on the dithiane chemistry developed by Corey and Seebach,[6a,b] and in particular its recent association with the Brook rearrangement by Smith et al. to accomplish bidirectional fragment coupling (anion relay chemistry or "ARC").[6c−e]

In all the various enolate-type alkylation reactions, the yield generally decreases rapidly with an increase in the chain length of the alkylating agent, unless a particularly activating feature is present as in allylic, benzylic, and propargylic halides or sulfonates. Furthermore, the presence of many common polar groups on the alkylating partner is usually not tolerated. We discovered some time ago that xanthates (dithiocarbonates) of general formula R-S(C═S)OEt can add to unactivated alkenes by a radical chain process.[7] In the case of *S*-(2-oxoalkyl)-xanthates **8**, the addition leads to highly functional ketones **10** (Scheme 2).

Scheme 2. Radical Addition of *S*-(α-Ketonyl)-Xanthates



This transformation thus corresponds to a formal alkylation of a ketone. We also found that a double addition to an alkene is

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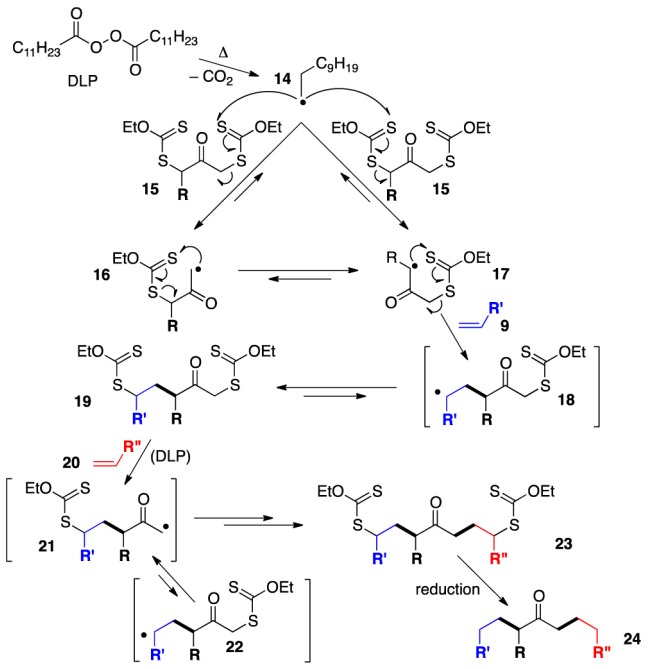
possible starting with bis-xanthate **11**, as illustrated by its reaction with vinyl tris(*t*-butoxy)silane, furnishing symmetrically substituted ketone **13** after reductive dexanthylation of the initial adduct **12** (Scheme 2).[8] This represents an instance of a symmetrical distal (or α,α'-) formal dialkylation of acetone. For the formal unsymmetrical dialkylation of acetone, we used *S*-(3-chloro-2-oxo-propyl)-*O*-ethyl xanthate to fashion ketones of general structure **2** (R = H).[9] We now propose a solution for the more challenging and synthetically more significant construction of branched unsymmetrical ketones **2** (R ≠ H).

Our conception is outlined in Scheme 3. Thus, the undecyl radical **14** generated upon thermolysis of dilauroyl peroxide

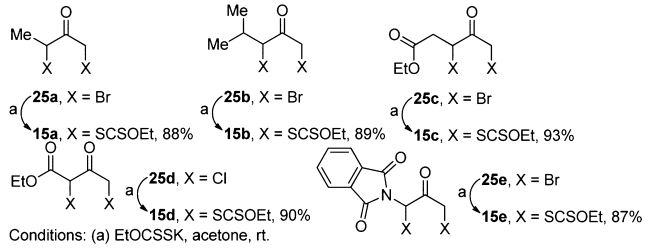
Scheme 3. Addition of Branched *S*-(α-Ketonyl)-Xanthates



(DLP), the usual initiator for these radical reactions, will attack both xanthates in unsymmetrical dixanthate **15** with essentially equal probability. Because of delocalization of the unpaired electron onto the carbonyl group, both ensuing radicals **16** and **17** are much more stable than the primary undecyl radical and will therefore be produced also with equal probability. However, radicals **16** and **17** are themselves in rapid equilibrium through exchange (most likely intramolecular) of the xanthate. The equilibrium will reflect the relative stability of radicals **16** and **17** and will be normally in favor of the latter, since most substituents R will stabilize the radical species. A simple alkyl group will thus provide a 3–4 kcal/mol stabilization, and consequently, according to the Arrhenius equation, the steady-state concentration of radicals **17** will be at least a hundred times greater than that of the less stable isomeric radical **16**.[10] The result is that the addition leading to adduct **18** will be greatly favored over the alternative arising from addition of radical **16**. Therefore, by using alkene **9** as the limiting reagent, the radical addition should preferentially furnish adduct **19**. This product still possesses two xanthate groups, and by the same reasoning, its exposure to a second alkene **20** will selectively afford adduct **23** because it is radical **21** that is now much more stable than radical **22** (the exchange is intermolecular in this case). After reductive removal of the two xanthate groups, the overall result is a formal unsymmetrical dialkylation of unsymmetrical ketone **1** into structurally much more complex ketone **24**.

In order to test the feasibility of this approach to unsymmetrical ketones, five dixanthates **15a–e** were prepared by reacting the corresponding known dihalides **25a–d** with EtOCSSK in acetone (Scheme 4).[11] Compounds **15a** and **15b**

Scheme 4. Synthesis of Xanthates 15a–e[a]



[a]Conditions: (a) EtOCSSK, acetone, rt.

were selected to see if a simple alkyl group is capable of exerting the desired control on the regioselectivity. In the case of **15b**, there was the possibility that the significant increase in steric hindrance due to the isopropyl group could counteract the small radical stabilization and degrade the regioselectivity. Both **15a** and **15b** would be valuable reagents for the synthesis of terpenes, because of the ubiquity of methyl and isopropyl groups in this class of natural substances. Compounds **15c–e** were chosen to illustrate the possibility of obtaining highly functional unsymmetrical ketones not readily accessible by classical enolate chemistry.

In the event, the regioselective sequential dialkylation proceeded very cleanly, as demonstrated by the very diverse examples in Schemes 5 and 6. The former displays additions starting with methyl- and isopropyl-substituted bis-xanthates **15a** and **15b** (products **24a–m**), whereas the latter shows additions from the more functionalized bis-xanthates **15c–e** (products **24n-ab**). In the first step leading to adducts **19a–v**, the alkene partner was used as the limiting reagent to avoid a second radical addition taking place from the unwanted side of the ketone. In the next addition, it is the xanthate that was employed as the limiting reagent. Finally, both xanthate groups in **23a–ab** were reductively removed in order to simplify the characterization. We have used three methods for the reduction: (a) Barton's hypophosphorus reagent,[12] (b) stoichiometric lauroyl peroxide in isopropanol,[13] and (c) tris(trimethylsilyl)silane.[14] For the sake of clarity, the yields for all three steps are given, but only the structures of the dexanthylated products **24a** to **24ab** are depicted. The numbering adopted reflects the generic structures in Scheme 3; because the first adducts **19** were in a few cases used more than once, there are fewer compounds **19a–w** than **23a–ab** or **24a–ab**.

A glance at the structures in Schemes 5 and 6 gives immediately an idea of the remarkable tolerance for polar functional groups such as esters (including malonates), amides, imides, nitriles, free alcohols, and even MIDA boronates (e.g., **24i**)[15] as well as ketones (as in **24e–g** and **24u**). Most of the compounds shown would take many more steps to prepare by conventional enolate chemistry, in particular because of the need for various protection–deprotection steps and the incorporation of auxiliary groups to obviate problems of regiochemistry. Furthermore, while we have separated the three steps for convenience, this is not necessary in principle. For example, all three steps leading to compound **24s** could be carried out in one pot without isolation

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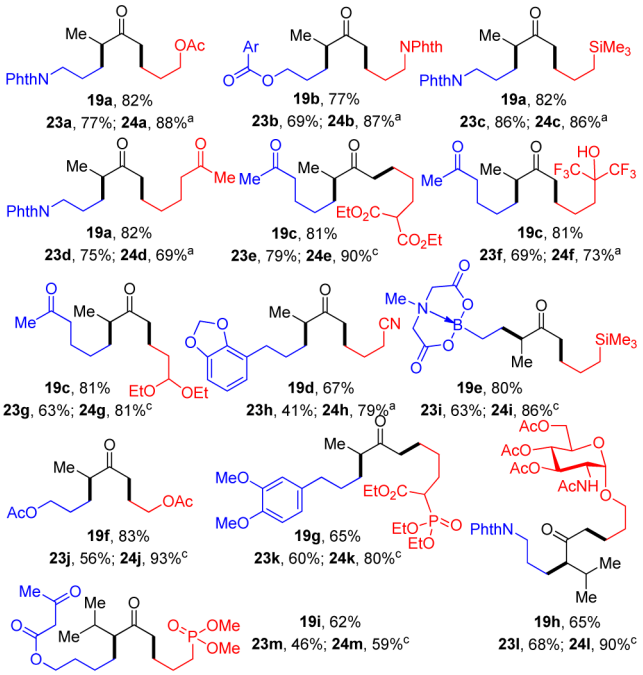
Scheme 5. Examples of Formal Unsymmetrical Dialkylation of Ketones Derived from Xanthates 15a and 15b[a]



PhthN = phthalimide; Ar = *p*-ClC_6H_4-
Reducing conditions: a) H_3PO_2, Et_3N, (AIBN), dioxane, reflux; b) isopropanol, lauroyl peroxide (stoichiometric); c) $(Me_3Si)_3SiH$, (AIBN), toluene, reflux.

[a]PhthN = phthalimide; Ar = *p*-ClC_6H_4. Reducing conditions: a) H_3PO_2, Et_3N, (AIBN), dioxane, reflux; (b) isopropanol, lauroyl peroxide (stoichiometric); (c) $(Me_3Si)_3SiH$, (AIBN), toluene, reflux.

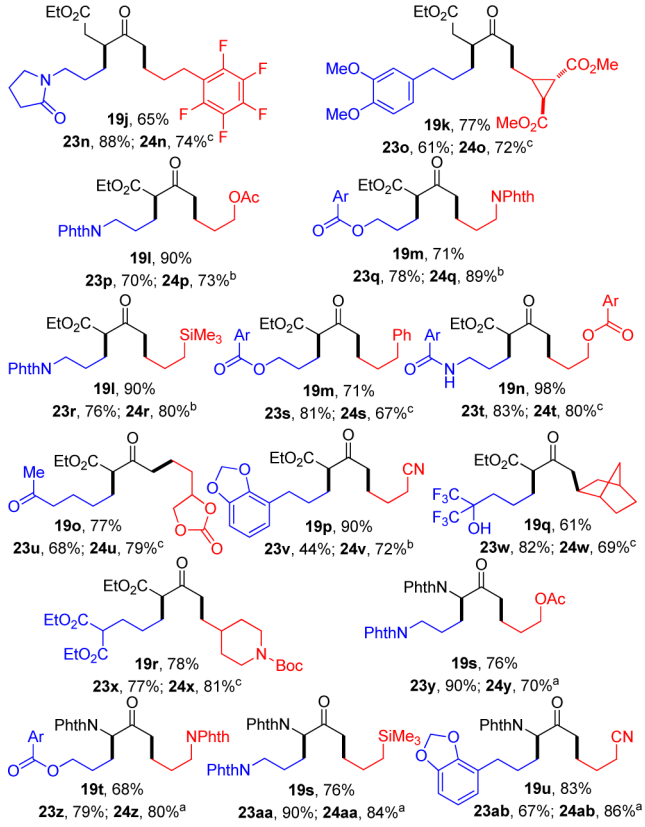
of intermediates **19m** and **23s** in an overall yield that was even slightly better (43% vs 39%).

The ability to attach together so many different functional groups allows for numerous further synthetic modifications. For instance, compounds **24m** and **24k** in Scheme 5 contain a ketone and a phosphonate ideally positioned for an intramolecular Horner–Wadsworth–Emmons condensation leading to a cyclohexenecarboxylate. Alternatively, liberating the amine from the phthalimido group in **24a,b,l,p,z** should result in spontaneous ring-closure onto the ketone to give the corresponding cyclic imines (or piperidines upon reduction). Two less obvious transformations are outlined in Scheme 7. In the first, exposure of ketone **23ac** to the combined action of benzylamine and *p*-TSA gives pyrrole **26**,[16] without affecting the remaining xanthate group.

In the second sequence, ketoester **24s** is converted into isoxazolinone **27** and then into alkyne **28** by a mechanistically fascinating process we described some years ago (Scheme 7).[17] The association of the xanthate addition with the nitrosative cleavage makes xanthate **15d** the synthetic equivalent of unknown diradical **29**, a species that would be too difficult to generate and handle.

In summary, by exploiting the exquisite control exerted by the xanthate function on the relative concentrations of the various radicals in the medium, we have succeeded in implementing a powerful strategy for the synthesis of unsymmetrically substituted ketones that avoids many of the problems associated with the classical ionic and transition-metal-based approaches. In view of the central position of ketones in organic synthesis, the present carbon–carbon bond forming process acquires a particular strategic importance and might well represent a paradigm shift in the way substituted ketones are constructed.[18]

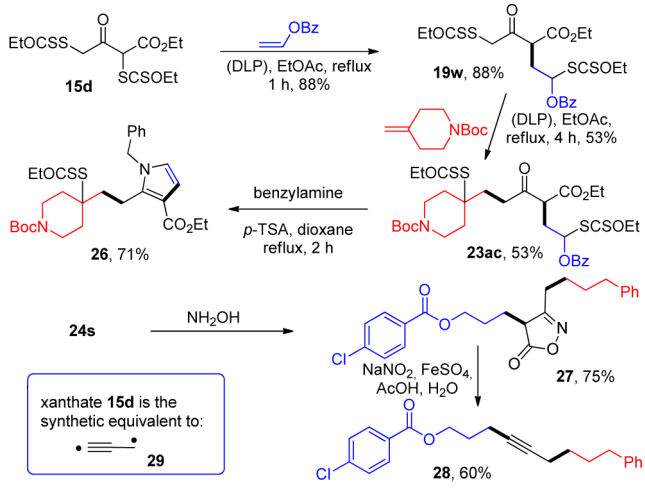
Scheme 6. Examples of Formal Unsymmetrical Dialkylation of Ketones Derived from Xanthates 15c–e[a]



PhthN = phthalimide; Ar = *p*-ClC_6H_4-
Reducing conditions: a) H_3PO_2, Et_3N, (AIBN), dioxane, reflux; b) isopropanol, lauroyl peroxide (stoichiometric); c) $(Me_3Si)_3SiH$, (AIBN), toluene, reflux.

[a]PhthN = phthalimide; Ar = *p*-ClC_6H_4. Reducing conditions: (a) H_3PO_2, Et_3N, (AIBN), dioxane, reflux; (b) isopropanol, lauroyl peroxide (stoichiometric); (c) $(Me_3Si)_3SiH$, (AIBN), toluene, reflux.

Scheme 7. Further Synthetic Transformations



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05344.

Experimental procedures as well as a compilation of spectral and analytical data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews, see: (a) *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000. (b) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 1−63. (c) Carine, D. In *Carbon-Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1989; Vol. *1*, pp 85−352.

(2) For reviews, see: (a) Huang, F.; Liu, Z.; Yu, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 862. (b) Obora, Y. *ACS Catal.* **2014**, *4*, 3972. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (d) Pan, S.; Shibata, T. *ACS Catal.* **2013**, *3*, 704. (e) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (f) Alonso, F.; Foubelo, F.; Gonzalez-Gomez, J. C.; Martinez, R.; Ramon, D. J.; Riente, P.; Yus, M. *Mol. Diversity* **2010**, *14*, 411. For selected recent examples see: (g) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. J.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664. (h) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1642. (i) Quan, X.; Kerdphon, S.; Andersson, P. G. *Chem. - Eur. J.* **2015**, *21*, 3576. (j) Chan, L. M. K.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 761. (k) Li, F.; Ma, J.; Wang, N. *J. Org. Chem.* **2014**, *79*, 10447. (l) Ogawa, S.; Obora, Y. *Chem. Commun.* **2014**, *50*, 2491. (m) Yan, F.-X.; Zhang, M.; Wang, X.-T.; Xie, F.; Chen, M.-M.; Jiang, H. *Tetrahedron* **2014**, *70*, 1193. (n) Iuchi, Y.; Hyotanishi, M.; Miller, B. E.; Maeda, K.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2010**, *75*, 1803. (o) Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, *4*, 116. (p) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913. (q) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72.

(3) (a) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337. (b) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362. For reviews, see: (c) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253. (d) Lazny, R.; Nodzewska. *Chem. Rev.* **2010**, *110*, 1386. For recent applications, see: (e) Sharpe, R. J.; Portillo, M.; Vélez, R. A.; Johnson, J. S. *Synlett* **2015**, *26*, 2293. (f) Sharpe, R. J.; Johnson, J. S. *J. Org. Chem.* **2015**, *80*, 9740. (g) Geden, J. V.; Beasley, B. O.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2013**, *78*, 12243. (h) Geden, J. V.; Beasley, B. O.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2013**, *78*, 12243. (i) He, Z.; Zajdlik, A.; St. Denis, J. D.; Assem, N.; Yudin, A. K. *J. Am. Chem. Soc.* **2012**, *134*, 9926. (j) Hazelard, D.; Fadel, A. *Tetrahedron: Asymmetry* **2005**, *16*, 2067.

(4) (a) Hauser, C. R.; Harris, T. M. *J. Am. Chem. Soc.* **1958**, *80*, 6360. (b) Wolfe, J. F.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3249. (c) Hampton, K. G.; Hauser, C. R. *J. Org. Chem.* **1965**, *30*, 2934. For review, see: (d) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065.

(5) (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Wagner, F.; Harms, K.; Koert, U. *Org. Lett.* **2015**, *17*, 5670.

(6) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (b) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077. (c) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. For review, see: (d) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (e) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883. For more recent approaches, see: (f) Heller, S. T.; Newton, J. N.; Fu, T.; Sarpong, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 9839. (g) Le, C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 11938. (h) Shneider, O. S.; Pisarevsky, E.; Fristrup, P.; Szpilman, A. M. *Org. Lett.* **2015**, *17*, 282. (I) Willwacher, J.; Kausch-Busies, N.; Fürstner, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12041.

(7) Reviews: Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2010**, *83*, 519. (b) Quiclet-Sire, B.; Zard, S. Z. *Top Curr. Chem.* **2006**, *264*, 201. For an account of the discovery of this process, see: (c) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663.

(8) Quiclet-Sire, B.; Yanagisawa, Y.; Zard, S. Z. *Chem. Commun.* **2014**, *50*, 2324.

(9) (a) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006**, *4*, 278. (b) de Greef, M.; Zard, S. Z. *Org. Lett.* **2007**, *9*, 1773.

(10) Hioe, J.; Zipse, H. *Org. Biomol. Chem.* **2010**, *8*, 3609.

(11) Synthesis of dihalides: (a) **25a** and **25b**: De Kimpe, N.; D'Hont, L.; Mones, L. *Tetrahedron* **1992**, *48*, 3183. **25c**: (b) Zimmer, R.; Collas, M.; Roth, M.; Reißig, H.-U. *Liebigs Ann. Chem.* **1992**, *1992*, 709. (c) **25d**: Reid, R. C.; Yau, M.-K.; Singh, R.; Lim, J.; Fairlie, D. *J. Am. Chem. Soc.* **2014**, *136*, 11914. (d) **25e**: Walters, M. A.; Arcand, H. *J. Org. Chem.* **1996**, *61*, 1478.

(12) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645.

(13) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877.

(14) Chatgilialoglu, C. *Chem. Rev.* **1995**, *95*, 1229.

(15) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2015**, *137*, 6762.

(16) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, *34*, 75.

(17) For a review, see: Zard, S. Z. *Chem. Commun.* **2002**, 1555.

(18) The same factors should also allow the unsymmetrical fragment coupling to operate with other electron-withdrawing groups, such as esters, nitriles, amides, etc.

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