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Transition-Metal-Free C-Arylation at Room Temperature by Arynes

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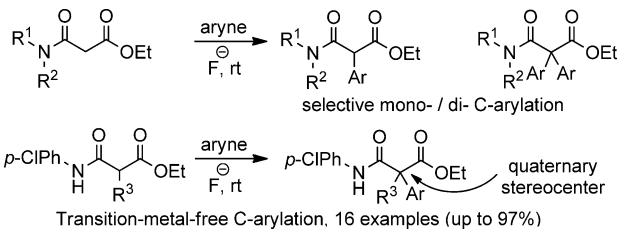
ABSTRACT

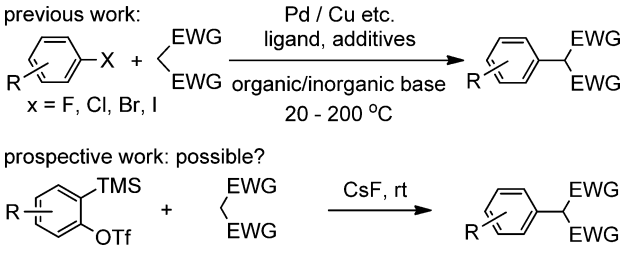


A facile, fluoride-induced transition-metal-free chemoselective α-arylation of β-dicarbonyl compounds (malonamide esters) at room temperature using aryne intermediates has been demonstrated. Selective mono- or diarylation and generation of a quaternary benzylic stereocenter have also been achieved. The methodology will be highly useful for the synthesis of a library of CNS depressant barbiturate drugs like Phenobarbital.

The α-arylation of β-dicarbonyl compounds has become a widely used method,[1,2] which provides an easy access to important classes of biologically active natural/synthetic products.[3] This transformation is usually carried out by transition-metal-catalyzed[1] (Scheme 1) or rarely by organomediated[2] reactions. Introduction of the "Benzyne" species[4] in 1953 by Roberts et al. opened up a new avenue for chemists to explore.

Particularly, fluoride-induced milder reaction conditions[5] for in situ generation of arynes have captured the attention of synthetic organic chemists. Since then the high reactivity of arynes due to its distinct electrophilicity has been utilized efficiently and has resulted in a diverse range of useful compounds including complex bioactive natural products.[6] The most commonly observed and well studied reactions are the insertion of arynes into

Scheme 1. Previous and Prospective C-Arylation



(1) (a) Huang, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1028. (b) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (d) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269. (e) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541. (f) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(2) (a) Alemán, J.; Richter, B.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5449. (b) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (c) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510.

(3) α-Aryl acids/malonates (modulators in mammalian membranes): (a) Beyer, J.; Jensen, B. S.; Strøbæk, D.; Christophersen, P.; Teuber, L. WO Patent 00/37422, 2000. Chloropeptin I and II: (b) Hegde, V. R.; Dai, P.; Patel, M.; Gullo, V. P. *Tetrahedron Lett.* **1998**, *39*, 5683. Lucuminic acid: (c) Takeda, T.; Gonda, R.; Hatano, K. *Chem. Pharm. Bull.* **1997**, *45*, 697. Polymastiamide A: (d) Kong, F.; Andersen, R. J. *J. Org. Chem.* **1993**, *58*, 6924. Vulculic acid: (e) Kimura, Y.; Nishibe, M.; Nakajima, H.; Hamasaki, T. *Agric. Biol. Chem.* **1991**, *55*, 1137. (f) Nonsteroidal anti-inflammatory drugs: Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095. Vancomycin: (g) Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223.

(4) Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290.

(5) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

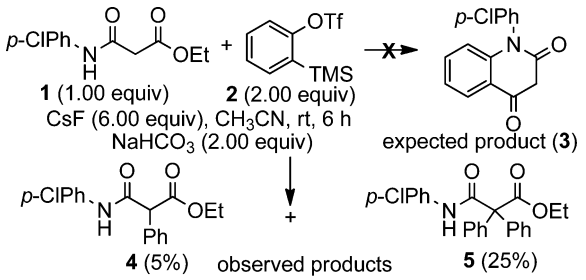
(6) For recent reviews on arynes, see: (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (b) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (c) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (d) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (e) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (f) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502.

10.1021/ol301768r

the element−element σ-bond and π-bond;[6,7] however examples of aryne insertion into the C−H σ-bond to directly provide C-arylated products are rare and to date are known for only a few substrates such as anilines,[8] aldehydes,[9] and β-enamino esters/ketones.[10] A literature survey revealed that in the case of α-unsubstituted β-dicarbonyl compounds Stoltz et al.[11] and Yoshida et al.[12] have observed the insertion of benzyne into the C−C σ-bond as the only product. Stoltz et al. also noticed the C-arylation as a side product only on α-methyl β-keto ester.[11] Wang et al. have reported[13] CuBr-trichloroacetic acid catalyzed C-arylation on 1,3-diones using anthranilic acid and isoamylnitrite at 60 °C, and Leake et al. reported phenylation of dialkyl malonates using bromobenzene and sodium amide in poor yields.[14]

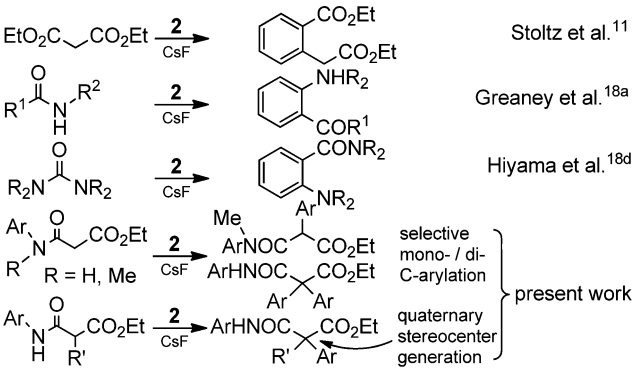
While working on a methodology development project, we carried out a reaction of malonamide ester[15] **1** (1.00 equiv) with benzyne precursor **2**[16] (2.00 equiv) in the presence of CsF (6.00 equiv) and $NaHCO_3$ (2 equiv) using

Scheme 2. Initial Studies on Aryne Methodology



acetonitrile as a solvent at rt (Scheme 2). We were expecting the quinolinedione compound **3**; however, to our surprise we observed only C-arylated products **4** and **5**. A general reactivity pattern of arynes with active methylene compounds[11,12,17] and amides[18] as observed in the literature is depicted in Scheme 3.

Scheme 3. Aryne Reactivity and Present Work



In view of the literature precedent (Scheme 3) the chemoselective C-arylation at milder reaction conditions on substrate **1** was intriguing and prompted us to take up further investigations. Reported herein are studies on the C-arylation of malonamide esters[15] and its application. Complete consumption of the substrate **1** and monoarylated product **4** was considered as the reference point during the optimization of the protocol. Several attempts (Table 1, entries 1−7) using varying ratios of substrate, CsF, silyl triflate **2**, and organic/inorganic bases always provided a mixture of **4**, **5**, and **1**. We conducted one reaction (Table 1, entry 8) without any base and by using an excess amount of CsF. Gratifyingly, **1** and **4** were completely consumed within 4 h to provide a 70% yield of product **5**. Further optimizations provided the best reaction conditions (Table 1, entry 10), which provided exclusively **5** in high yields (86%). Use of 18-crown-6 ether (Table 1, entry 11) gave only a 63% yield.

The optimized arylation protocol (Table 1, entry 10) was used for screening malonamide esters[15] (Tables 2 and 3) in the search for a more reactive and selective substrate. First, malonamide esters containing primary aromatic amines (Table 2, entries 2−6) were tested. With a simple phenylmalonamide ester (Table 2, entry 2) the corresponding diarylated product was obtained in 72% yield. Malonamide ester (*p*-methoxyphenylmalonamide ester) containing an electron-donating group provided the expected diarylated product in 75% yield (Table 2, entry 3). A further increase in electron-donating groups on the aromatic amine (Table 2, entry 4) did not show an improvement in the yield. Interestingly with *p*-toludine as the aromatic amine (Table 2, entry 5) only a 55% yield of the diarylated product was observed, and with *p*-nitroaniline as the aromatic amine (Table 2, entry 6), though the reaction was fast, the yield reduced to 46%. Malonamide esters containing aliphatic primary amines (Table 2, entries 7−9) were also studied. The malonamide ester containing

(7) Selected references on recent developments in aryne chemistry: (a) Hamura, T.; Chuda, Y.; Nakatsuji, Y.; Suzuki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 3368. (b) Lu, C.; Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2279. (c) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2743. (d) Rodríguez-Lojo, D.; Cobas, A.; Peña, D.; Pérez, D.; Guitián, E. *Org. Lett.* **2012**, *14*, 1363. (e) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (f) Yoshida, H.; Asatsu, Y.; Mimura, Y.; Ito, Y.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9676.

(8) Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1006.

(9) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

(10) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.

(11) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.

(12) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292.

(13) Yang, Y.-Y.; Shou, W.-G.; Wang, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 8163.

(14) Leake, W. W.; Levine, R. *J. Am. Chem. Soc.* **1959**, *81*, 1627.

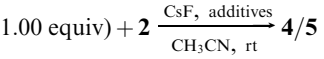
(15) Please see Supporting Information.

(16) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

(17) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729.

(18) Selected references on the reaction of amides with arynes: (a) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (b) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (c) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (d) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247.

Table 1. Optimization of the Arylation Protocol



entry	**2** (equiv)	CsF (equiv)	additives (equiv)	time (h)	**4/5**, yield (%)
1	2.00	6.00	$NaHCO_3$ (1.0)	6	5/25
2	2.00	8.00	$NaHCO_3$ (1.0)	20	7/26
3	2.00	4.00	$NaHCO_3$ (1.0)	24	10/20
4	2.00	12.00	TEA (1.0)	12	5/55
5	4.00	5.00	TEA (1.0)	13	30/5
6	4.00	6.00	TEA (1.0)	12	35/5
7	4.00	6.00	TEA (1.0)	48	35/5
8	2.50	15.00	–	4	0/70
9	3.30	16.50	–	4	0/75
10	**4.00**	**8.00**	–	**5**	**0/86**
11	4.00	8.00	18-crown-6 (2.0)	6	5/63

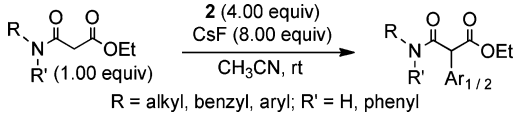
benzylamine (Table 2, entry 7) was quite reactive but provided the expected diarylated product in only a 40% yield. The other two malonamide esters containing primary aliphatic moieties (Table 2, entries 8 and 9) could not furnish any useful product. Then the effect on malonamide ester containing secondary aliphatic/aromatic amines (Table 2, entries 10 and 11) was studied. Diphenylmalonamide ester (Table 2, entry 10) was less reactive and provided only a 50% yield of the diaryl product. In the case of the dialkyl amine containing substrate (Table 2, entry 11), we could not see any useful product. Monoalkyl or dialkyl malonamides (Table 2, entries 8, 9, 11) fail to give any product plausibly because methylene protons are less acidic than aryl malonamides.

Malonamide ester **6** (Table 3, entry 1), which is a combination of an aromatic−aliphatic amine, interestingly provided only the monoarylated product in 90% yield. This observation was confirmed by the treatment of **6** with various aryne precursors **7/8** (Table 3, entries 2 and 3), and in those cases also, the only corresponding monoaryl products were obtained in 55% and 62% yields respectively. The acidity of methylene protons in the malonamide ester **6** is finely balanced between mono/dialkyl malonamides and aryl malonomides, which probably results in selective monoarylation. The screening study (Tables 2 and 3) provided two important substrates, **1** (for diarylation) and **6** (for selective monoarylation). Though substrate **1** emerged as the best for diarylation among the other substrates under study, we believe that further screening of malonamide esters containing aromatic amines with other halide substituents might provide a more reactive substrate than ester **1**.

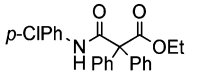
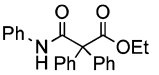
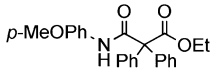
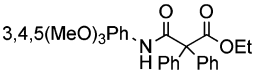
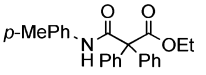
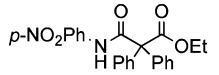
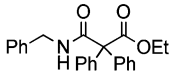
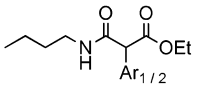
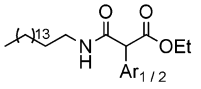
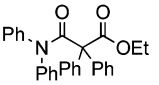
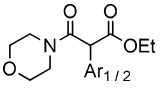
We envisaged that the arylation protocol could be applied for the generation of racemic quaternary stereocenters, which are found in several important molecules in medicinal

(19) (a) Christoffers, J., Baro, A., Eds. *Quaternary Stereocenters - Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

Table 2. Screening of Malonamide Esters



R = alkyl, benzyl, aryl; R' = H, phenyl

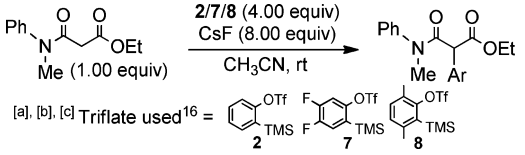
entry	product	time (h)	yield (%)
1		05	86
2		06	72
3		06	75
4		06	70
5		06	55
6		02	46
7		02	40
8		11	–
9		10	–
10		06	50
11		12	–

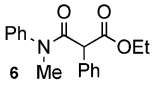
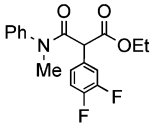
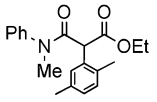
applications and in many natural products.[19] The construction of such quaternary stereocenters is a much more demanding and challenging task.[20] α-Substituted malonamide esters[15,21] containing *p*-chloroaniline were used. The α-methyl substituted malonamide ester (Table 4, entry 1) provided the corresponding arylated compound in 85% yield; however the α-ethyl substituted substrate (Table 4, entry 2) provided the expected compound in very high yields (92%). The α-butyl substituted substrate (Table 4, entry 3) provided the expected compound in quantitative yields (97%). Similarly the α-benzyl substituted malonamide ester provided the expected arylated product (Table 4, entry 4) in excellent yields (90%). Arylation of the α-phenyl substituted

(20) (a) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M.-H.; Jew, S.-S.; Park, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 4924. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

(21) α-Substituted malonamide ester preparation: (a) Peng, B.; Zhang, S.; Yu, X.; Feng, X.; Bao, M. *Org. Lett.* **2011**, *13*, 5402. (b) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469. (c) Keglevich, G.; Novák, T.; Vida, L.; Greiner, I. *Green Chem.* **2006**, *8*, 1073 and references cited therein.

Table 3. Substrate for Selective Monoarylation



entry	product	time (h)	yield (%)
1[a]		12	90
2[b]		8	55
3[c]		10	62

substrate with 3,4-difluorinated aryne precursor **7** furnished the expected product in 60% yield (Table 4, entry 5). Interestingly all the compounds synthesized by this methodology (Tables 2–4) are new,[22] and analogues of these compounds are very well-known sedative-tranquillizers.[23] The products obtained in Tables 2 and 3 can also serve as important precursors to CNS depressant barbiturates drugs. Phenobarbital is one of the most widely used anticonvulsant barbiturate drugs,[24] and using simple organic transformations,[25] its synthesis should be possible starting from the product **9** (Table 4, entry 2) obtained by our methodology. Similarly a library of such compounds can be prepared for SAR studies.

In conclusion, we have disclosed the application of aryne chemistry for the α-arylation of α-substituted/unsubstituted

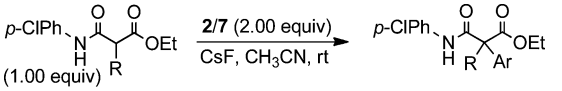
(22) The product of entry 1 (Table 3) is known, but its synthesis is not reported: Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249.

(23) Loev, B.; Macko, E.; Fried, I. M. *J. Med. Chem.* **1969**, *12*, 854.

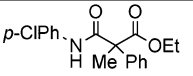
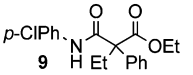
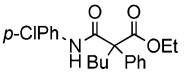
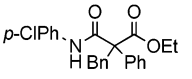
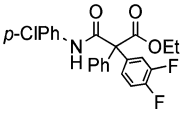
(24) (a) "WHO Model List of Essential Medicines". World Health Organization. March 2005. http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf. (b) Kwan, P.; Brodie, M. J. *Epilepsia* **2004**, *45*, 1141.

(25) (a) Glatzhofer, D. T.; Roy, R. R.; Cossey, K. N. *Org. Lett.* **2002**, *4*, 2349. (b) Yoon, J. H.; Park, Y. J.; Lee, J. H.; Yoo, J.; Jun, C.-H. *Org. Lett.* **2005**, *7*, 2889. (c) Arai, K.; Tamura, S.; Kawai, K.-i.; Nakajima, S. *Chem. Pharm. Bull.* **1989**, *37*, 3117.

Table 4. Generation of Quaternary Stereocenters



R = methyl, ethyl, butyl, benzyl, phenyl; Ar = Ph-, 3,4(F)$_2$Ph-

entry	triflate-CsF 2 equiv-equiv	product	time (h)	yield (%)
1	**2**-5.00		5	85
2	**2**-7.00		6	92
3	**2**-6.00		5	97
4	**2**-6.00		5	90
5	**7**-5.00		5	60

malonamide esters. The preferential chemoselective C-arylation over the N-arylation/aryne insertion into the C–N σ-bond, the formation of selective mono- or diarylated products, and an easy access to compounds containing racemic benzylic quaternary stereocenters are noteworthy. The generalization work and application of the present methodology to the total synthesis of drugs and bioactive natural products is in progress.

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Supporting Information Available. Experimental details, analytical and spectra data as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.