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Radical-Based Arylation Methods

Homolytic Aromatic Substitution

Benjamin Wyler Topic Review in Group Renaud 03.04.2014





Literature



- Studer, A.; Bossart, M. in *Radicals in Organic Synthesis*, Vol. 2, eds P. Renaud, M. P. Sibi, Wiley-VCH Verlag GmbH, Weinheim, 2001, 62–80.
- Vaillard, S. E.; Schulte, B.; Studer, A. in *Modern Arylation Methods*, ed. L. Ackermann, Wiley-VCH Verlag GmbH, Weinheim, 2009, 475–535.
- Vaillard, S. E.; Studer, A. in *Encyclopedia of Radical in Chemistry, Biology and Materials,* Online, eds C. Chatgilialoglu, A.Studer, John Wiley & Sons, Ltd., 2012.
- Studer, A.; Bossart, M. Tetrahedron 2001, 57, 9649–9667. (Radical aryl migration reactions)



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S_{RN}1 Reactions (Unimolecular Radical Nucleophilic Substitution)

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ArX + Nu^{_} (1)→ ArNu + X⁻ INITATION Nu ArX + Donor (ArX) • -(2) e-PROPAGATION ΕT EΤ (ArX) •-→ Ar[•] + X⁻ (3) (ArNu)^{•–} Ar• + Nu− ___ (4) Х-Nu $(ArNu)^{\bullet-} + ArX \longrightarrow (ArX)^{\bullet-} + ArNu$ (5) Nu⁻ **TERMINATION** $(ArNu)^{\bullet-} + Ar^{\bullet-} \rightarrow ArNu + Ar^{-}$ (6) + SolvH Ar[•] ArH + Solv[•] (7)

Bardagí, J. A.; Vaillard, V. A.;Rossi, R. A. in *Encyclopedia of Radical in Chemistry, Biology and Materials,* 5 Online, eds C. Chatgilialoglu, A. Studer, John Wiley & Sons, Ltd., 2012.



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Several different possible mechanism were proposed by A. K. J. Beckwith, **1995**

- I. Disproportionation or hydrogen-atom transfer from Bu₃SnH followed by oxidation of cyclohexadiene derivatives during work-up
- II. 'pseudo' S_{RN}1 mechanism (as proposed by Bowman *et al. Tetrahderon* **1991**, *47*, 10119)
- III. Oxidation of cyclohexadiene radical by AIBN (suggested by Curran *et al. Tetrahedron* **1994**, *50*, 7343)



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 Disproportionation or hydrogen-atom transfer from Bu₃SnH followed by oxidation of cyclohexadiene derivatives during work-up



- yield higher than 50%
- no D-incorporation when using Bu₃SnD
- Oxidation of dihydro-type systems as **B** is not fast in this system



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II. 'pseudo S_{RN} 1' mechanism (as proposed by Bowman *et al.*)

$$ArRH^{\bullet} + Bu_3SnH \longrightarrow [Ar-R]^{\bullet-} + Bu_3Sn^+ + H_2$$
 (1)

$$[Ar-R]^{\bullet-} + Ar-X \longrightarrow Ar-R + [Ar-X]^{\bullet-}$$
(2)

$$[Ar-X]^{\bullet-} \rightarrow Ar^{\bullet} + X^{-}$$
(3)

- if equation (1) is involved, with deuterated compound **D** HD should be formed
- no HD detected in mass spectrometry, NMR or Raman spectroscopy



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III. Oxidation of cyclohexadiene radical by AIBN (as suggested by Curran *et al.*)



- Bu₃SnH not regenerated (x = 2.2 to 0.5, y = 1.0) → no
 hydrogen-atom transfer between Bu₃Sn[•] and ArRH[•]
- Stochiometric amount of "initiator" needed (x = const., y = various, if y < 1.0 → incomplete)
- in cyclization reactions with 1.1 eq. Bu_3SnH and 1.3 eq. of AIBN, only 0.3 eq. N_2 was detected

$$E$$

$$AIBN: R = Me, Z = CN$$

$$AIBN: R = Et, Z = CN$$

$$AIBN: R = Et, Z = CN$$

$$AIBMe: R = Me, Z = CO_2Me$$

Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem.* **2004**, 10 *116*, 97–100; Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343–7366.



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III. Oxidation of cyclohexadiene radical by AIBN (as suggested by Curran *et al.*)



- reduced AIBN or AMBN derivates (G) are unstable and decompose
- reduced AIBMe derivative (G) was recently isolated from a Bu₃SnH-mediated cyclization onto pyrazole

(*Tetrahedron Letters* **2002**, *4*3, 4191–4193)

AIBN: R = Me, Z = CN

AMBN:
$$R = Et$$
, $Z = CN$

AIBMe: R = Me, $Z = CO_2Me$

Homolytic Aromatic Substituition

1. Intermolecular Substitution

1.1 Aromatic Substitution with Nucleophilic C-centered Radicals

1.2 Aromatic Substitution with Electrophilic C- and N-centered Radicals

1.3 *ipso* Substitution/Aryl Migration

2. Intramolecular Substitution

2.1 Aromatic Substitution with Aryl and Nucleophilic C-centered Radicals

2.2 Aromatic Substitution with Electrophilic C-centered Radicals

2.3 *ipso* Substitution/Aryl Migration



Addition to benzene



> Reaction of an nucleophilic radical with benzene



> Rate constant for the addition of *n*-butyl radical at 79 °C is 3.8 x 10² M⁻¹ s⁻¹. This is far below the rate of an efficient radical reaction → side reactions occurring!

Regioselectivity of radical addition to substituted benzene derivatives

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Substituent X	ortho	meta	para
OMe	38.0	31.0	31.0
CI	0	66.8	33.2
CO ₂ Me	0	4.5	95.5
CN	7.4	4.7	87.9

- (Regioselective) substitution of nucleophilic C-centered radicals only efficient on electron-poor benzene derivatives
- > Not synthetically useful

Minisci reaction (1970ies)



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I. Oxidative Decarboxylation with silver(I)salt and oxidizing reagent

R-COOH $AgNO_3$, $(NH_4)_2S_2O_8$, H_2SO_4 \rightarrow R \cdot + CO₂

II. Nucleophilic attack onto protonated arene



III. Oxidation/Rearomatization





Relative rates of Minisci reaction



х	Me*	Bu*	<i>s</i> Bu⁺	tBu*
CN	12.5	20.3	259.0	1890
COMe	3.6	5.6	55.6	144
Cl	2.4	-	-	11.1
н	1	1	1	1
Me	0.5	0.3	0.3	0.15
OMe	0.3	0.1	0.02	0.005

- > Electron-rich radical (R^{*}) and Electron-poor arene
- CH₂CN do not react with protonated pyridines

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Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem.* 18 Soc. **2010**, *132*, 13194–13196.

`Ar

N¹ H H

Zinc sulphinate salts as radical precursors for Minisci-type reaction





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> Zinc sulphinate salts by Baran and coworkers, **2012**

Zn		t-BuOOH		
$H=SU_2UI$ H_2U	→ (n-30 ₂)) ₂ ∠11	F n	
R group	Acronym	Amount prepared	Sigma–Aldrich catalogue number	
-CF ₃ (X-ray)	TFMS (A)	>500 g	L510106	
-CF ₂ H (X-ray)	DFMS (B)	>500 g	L510084	
-CH ₂ CF ₃	TFES (C)	>100 g	L511234	
-CH ₂ F	MFMS (D)	37 g	-	
-CH(CH ₃) ₂	IPS (E)	>200 g	L511161	
-(CH ₂ CH ₂ O) ₃ CH ₃	TEGS (F)	20 g	-	

Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Baran, P. S. *et al. Nature* **2012**, *492*, 95–99; Langlois, B. R.; Laurent, E.; 19 Roidot, N. *Tetrahedron Letters* **1991**, *32*, 7525–7528.



O'Hara, F.; Blackmond, D. G.; Baran, P. S. J. Am. Chem. Soc. 2013, 135, 12122–12134.

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O'Hara, F.; Blackmond, D. G.; Baran, P. S. J. Am. Chem. Soc. 2013, 135, 12122–12134.

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Predictable selectivity in CHCl₃/H₂O or CHCl₃/H₂O/TFA; innate reactivity dominates



> Predictable selectivity in DMSO; conjugate reactivity dominates



O'Hara, F.; Blackmond, D. G.; Baran, P. S. J. Am. Chem. Soc. 2013, 135, 12122–12134.

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> Tuning regioselectivity with solvent choice



O'Hara, F.; Blackmond, D. G.; Baran, P. S. J. Am. Chem. Soc. 2013, 135, 12122–12134.

1.1 Aromatic Substitution with Nucleophilic C-centered Radicals

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Radical-based regioselective C–H functionalization of electron-deficient heteroarenes



by Boehringer Ingelheim





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Manganese(III)acetate-initiated reaction

Heiba *et al.* **1969**

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Heiba, E.-A. I.; Dessau, R. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 138–145. Chuang, C. P.; Wang, S. F *Tetrahedron Letters* **1994**, *35*, 1283–1284.

Oxidation of Li-enolates and its application to natural product synthesis



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Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451; Baran, P. S.; Richter, J. M.; Lin, D. W. 27 *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 609–612.

Direct coupling of pyrroles with carbonyl compounds

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Intermolecular ipso substitution



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Requirements:

- > most often nucleophilic radicals in combination with electrophilic arenes
- replacing group should be small to allow *ipso* attack
- > must behave as a good radical leaving group



ipso substitution in benzothiazole



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X	conversion (%)	yield (%) ^a
NO ₂	100	95
PhSO ₂	100	80
PhSO	100	80
PhCO	100	55
MeS	50	60
MeO	10	40
Br	50	70

^a based on reacted SM





Pschorr reaction and its application

Intramolecular version of Gomberg-Bachmann reaction



Pschorr, R. *Berichte der deutschen chemischen Gesellschaft* **1896**, *29*, 496–501. Qian, X.; Mao, P.; Yao, W.; Guo, X. *Tetrahedron Letters* **2002**, *43*, 2995–2998.

Radical cyclization approach to spirocyclohexadienones



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González-López de Turiso, F.; Curran, D. P Org. Lett. 2005, 7, 151–154.



New 4+1 radical annulations

Curran, D. P.; Liu, H. J. Am. Chem. Soc. 1992, 114, 5863–5864.

hydroxymethylation, oxidation* (Danishefsky *JACS*, **1971, *93*, 5576)

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2.1 Aromatic Substitution with Aryl and Nucleophilic C-centered Radicals

A Flexible, Convergent Approach to Polycyclic Indole Structures: Formal Synthesis of (±)-Mersicarpine.

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Biechy, A.; Zard, S. Z. Org Lett 2009, 11, 2800–2803.

2.1 Aromatic Substitution with Aryl and Nucleophilic C-centered Radicals

Bu₃SnH, AIBN

PhH, Δ

R

Radical migration of substituents of aryl groups on quinazolinones derived from *N*-acyl cyanamides



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Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacôte, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, 37 *132*, 4381–4387.

2.1 Aromatic Substitution with Aryl and Nucleophilic C-centered Radicals

Radical migration of substituents of aryl groups on quinazolinones derived from *N*-acyl cyanamides



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	Substrate	Solvent	Product	Yield (%)
0	N N N	PhH	N N	45
		<i>t</i> -BuOH	N	47
	O <i>i</i> -Pr ↓ ↓	PhH	O <i>i</i> -Pr ↓ ↓	52
2 equiv. Bu ₃ SnH <i>slow addition (0.2 mmol/h)</i> 1.5 equiv. AIBN	N N <i>i</i> -Pr		<i>i</i> -Pr	
solvent, Δ	O CF ₃	PhH	O CF₃ ↓ ↓	24
	N N N F ₃ C	<i>t</i> -BuOH	F ₃ C	55
	O Me 	PhH	O Me ∦ ↓	58
R N		t-BuOH	H	69

Larraufie, M.-H.; Courillon, C.; Ollivier, C.; Lacôte, E.; Malacria, M.; Fensterbank, L. *J. Am. Chem. Soc.* **2010**, 38 *132*, 4381–4387.



2.2 Aromatic Substitution with Electrophilic C-centered Radicals

Tandem radical translocation and homolytic aromatic substitution

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One-pot homolytic aromatic substitutions/HWE olefinations



Teichert, A.; Jantos, K.; Harms, K.; Studer, A. Org. Lett. 2004, 6, 3477–3480.

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1,2-phenyl migration (neophyl rearrangement) to oxepines

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− Neophyl rearrangement is a relatively slow process ($k = 762 \text{ s}^{-1}$ at 25 °C) → used as radical clock



Kharasch, M. S.; Urry, W. H. *J. Am. Chem. Soc.* **1944**, *66*, 1438–1440; Cong, Z.; Miki, T.; Urakawa, O.; 43 Nishino, H. *J. Org. Chem.* **2009**, *74*, 3978–3981.



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A convergent radical-based route to biaryls

Quiclet-Sire, B.; Revol, G.; Zard, S. Z. Org. Lett. 2009, 11, 2832-2835.

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1,3-aryl migration from *N***- to** *C***-centered** radicals



2.3 ipso Substitution/Aryl Migration

1,4-aryl migration from C- to C-centered radicals (The intramolecular carboxyarylation approach to podophyllotoxin)



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1,4-aryl migration from sulfur in sulfonamides to carbon

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 First report on 1,4-aryl migration on sulfonamides by Speckamp and Loven



Novel Route to Biaryls by Motherwell and Pennell



Loven, R.; Speckamp, W. N. A *Tetrahedron Letters* **1972**, *13*, 1567–1570. Motherwell, W. B.; Pennell, A. M. K. J. Chem. Soc., Chem. Commun. **1991**, 877.

Domino radical cyclization/Smiles rearrangement combination (1,4-aryl migration)



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Stereoselective aryl migration from sulfonates to carbon (1,5-aryl migration)



Studer, A.; Bossart, M. Chem. Commun. 1998, 2127

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Stereoselective phenyl migration from silyl ethers to carbon (1,5-aryl migration)



Studer, A.; Bossart, M.; Steen, H. Tetrahedron Letters 1998, 39, 8829-8832.