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Radical Migration of Substituents of Aryl Groups on Quinazolinones Derived from *N*-Acyl Cyanamides

Marie-Hélène Larraufie, Christine Courillon,† Cyril Ollivier, Emmanuel Lacôte,* Max Malacria,* and Louis Fensterbank*

UPMC Univ Paris 06, Institut Parisien de Chimie Moléculaire (UMR CNRS 7201), C. 229, 4 Place Jussieu, 75005 Paris, France

Received December 17, 2009; E-mail: emmanuel.lacote@upmc.fr; max.malacria@upmc.fr; louis.fensterbank@upmc.fr

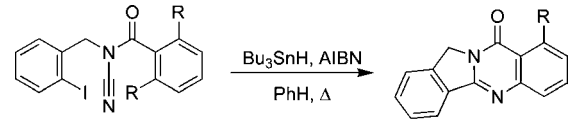
Abstract: A newly designed radical cascade involving *N*-acyl cyanamides is reported. It builds on aromatic homolytic substitutions as intermediate events and leads to complex heteroaromatic structures via an unprecedented radical migration of a substituent on aryl groups of quinazolinones (hydrogen or alkyl). Mechanistic considerations are detailed, which allowed us to devise fine control over the domino processes. The latter could be predictably stopped at several stages, depending on the reaction conditions. Finally, a surgical introduction of a trifluoromethyl substituent on a quinazolinone was achieved via the reported migration.

1. Introduction

Since the seminal total syntheses of (−)-heliotridine (Hart),[1] hirsutene (Curran),[2] and prostaglandin $F_{2\alpha}$ (Stork),[3] radical chemistry has been fully accepted in the forum of natural product synthesis.[4] In particular, radicals are well suited for rapid increase of molecular complexity from simple starting materials via domino processes.[5]

En route toward the total synthesis of luotonin A, we introduced *N*-acyl cyanamides as new radical acceptors.[6] This synthesis and the methodological examination that it spawned featured a final aromatic homolytic substitution (Scheme 1).[7]

Scheme 1. Formation of Quinazolinones via Radical Cascades

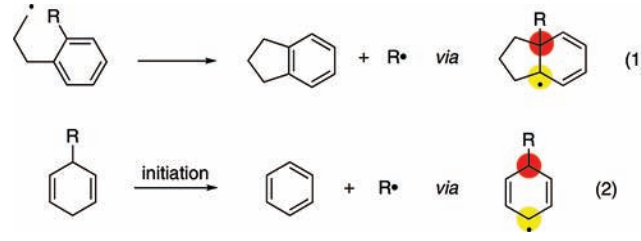


1a (R = H)
1b (R = Me)

2a, 71%
2b, 88%

Interestingly, when *o,o'*-dimethyl derivative **1b** was employed, a des-methyl quinozaline **2b** was isolated in high yield, presumably again via aromatic homolytic substitution.[8] In both cases, the homolytic substitution was the terminal process of the cascade. Equation 1 shows its general principle.

The radical extruded from the molecules after this kind of aromatization cannot be exploited for further complexity increase of the carbon skeleton.[9] Alternatively, a radical aromatization can be used to generate specially designed radicals without tin-containing reagents as illustrated by the recent work of Walton and Studer,[10] but in those cases the aromatic moiety was a byproduct that did not participate in further reactions (eq 2).



In this article, we report a newly designed radical cascade involving *N*-acyl cyanamides. It builds on aromatic homolytic

† Present address: Université Paris-Diderot, ITODYS (UMR CNRS 7086), Bâtiment Lavoisier, C. 7090, 15 rue Jean Antoine de Baïf, 75013 Paris, France.

(1) Hart, D. J. *Science* **1984**, *223*, 883–887.
(2) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943–3958.
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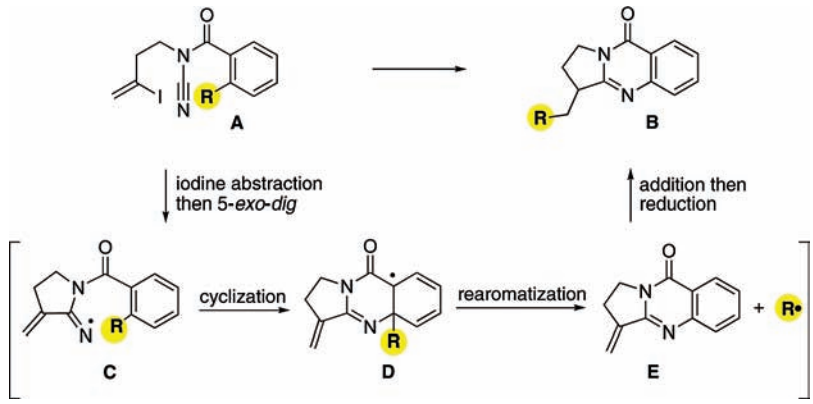
(4) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286. (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 405–407. (c) Aldabbagh, F.; Bowman, W. R. *Contemp. Org. Synth.* **1997**, 261–280. (d) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2. (e) Renaud, P. *Chimia* **2001**, *55*, 1045–1048.
(5) For reviews: (a) Albert, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Top. Curr. Chem.* **2006**, *264*, 1–62. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *118*, 7134–7186, See also: (c) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2683–2684. For contributions of our own group, see: (d) Rychlet Elliott, M.; Dhimane, A. L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427–3428. (e) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037–5038. (f) Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764–6765. (g) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856–3871.
(6) (a) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 576−579. For other (ionic) reactions involving cyanamides, see: (b) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3116–3120. (c) Giles, R. L.; Nkansah, R. A.; Looper, R. L. *J. Org. Chem.* **2010**, *75*, 261–264. Amidinyl radicals can also be formed directly: (d) Gennet, D.; Zard, S. Z.; Zhang, H. *Chem. Commun.* **2003**, 1870–1871.
(7) (a) Studer, A.; Bossart, M. *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germay, 2001; Vol. 2, pp 62−80. (b) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, 1803–1822.

Scheme 2. General Principle of the Radical Migration



substitutions as intermediate events and leads to complex heteroaromatic structures via an unprecedented radical migration of a substituent on aryl groups of quinazolinones (Scheme 2). We decided to introduce a suitably placed unsaturation of the quinazoline derived from our previous cascade (precursors of type **A**, Scheme 2). After iodine abstraction from the mediator and a regioselective 5-*exo-dig* cyclization, the *N*-iminyl radical **C** would undergo cyclization onto the aromatic ring. After rearomatization, the radical R• extruded from intermediate **D** would then re-add on **E** and lead to the formation of a new bond in **B**. Reasoning that aromatic moieties help groups additions onto conjugated double bonds, we thought that the best point of attachment for the unsaturation destined to participate to the final bond forming event was on the carbon between both nitrogen atoms.

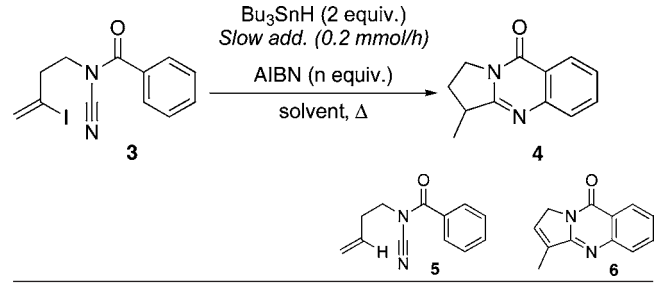
2. Reductions

Simple reductions (formal H• migrations) were examined first (Table 1).

In a typical experiment, vinyl iodide **3** was allowed to react with 2 equiv of tributyltin hydride (TBTH) in the presence of 1.5 equiv of AIBN in refluxing benzene. TBTH was added via syringe pump (0.2 mmol/h, entry 1). The desired quinazoline **4** was isolated in 66% yield along with 20% of a byproduct **6** arising from endocyclic migration of the double bond before final reduction. A rapid solvent screening indicated that a higher boiling solvent was detrimental (Entry 2). *tert*-Butanol gave the best isolated yields of **4** (77%, entry 3), with 12% of **6**. Interestingly, the quinazoline obtained are biologically active molecules or analogs thereof.[11]

Next, we focused on the amount of AIBN required. Indeed, stoichiometric amounts of AIBN are necessary in most cases

Table 1. Formal H• Migration



entry	solvent	*n*	yield of **4** (%)	byproducts
1	PhH	1.5	66	**6** (20%)
2	toluene	1.5	59[a]	**5** (18%)[a], **6** (15%)[a]
3	*t*-BuOH	1.5	77 (79)[a]	**6** (12%)[a]
4	*t*-BuOH	1	72[a]	**6** (13%)[a]
5	*t*-BuOH	0.5	64[a]	**5** (13%)[a], **6** (11%)[a]
6	*t*-BuOH	0.25	57[a]	**3** (6%)[a], **5** (8%)[a], **6** (10%)[a]

[a] NMR yields. Sulfolene was used as internal standard.

for rearomatization after radical addition to aryl moieties because AIBN presumably traps a H• from the intermediate radical bimolecularly to lead to the aromatization.[12] This mechanism was initially suggested by Curran,[12a] and Allin et al. were the first to evidence the key role azo initiators played as traps for the hydrogen atom transferred from radicals like **F** (Scheme 3). Aromatized product **G** was isolated together with hydrazine **H**.[13]

In our case, the H• formally adds onto the substrate (vide infra), so catalytic amounts of AIBN should have been sufficient for the reactions to proceed. Gradual lowering of the amount

(8) (a) Beaume, A.; Courillon, C.; Derat, E.; Malacria, M. *Chem. Eur. J.* **2008**, *14*, 1238–1252. For previous examples of aromatization prompted by alkyl and alkoxyl radical cleavage, see: (b) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S. *Tetrahedron* **1997**, *53*, 285–298. (c) Harrowven, W. D. C.; Nunn, M. I. T.; Newman, N. A.; Fenwick, D. R. *Tetrahedron Lett.* **2001**, *42*, 961–964. (d) Du, W.; Curran, D. P. *Synlett* **2003**, 1299–1302. (e) Bowman, W. R.; Fletcher, A. J.; Lovell, P. J.; Pedersen, J. M. *Synlett* **2004**, 1905–1908. (f) Binmore, G.; Cardellini, L.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 757–762.

(9) A rapid radical H-atom donor such as PhSeH can block the aromatization, see: Crich, D.; Grant, D.; Krishnamurthy, V.; Patel, M. *Acc. Chem. Res.* **2007**, *40*, 453–463.

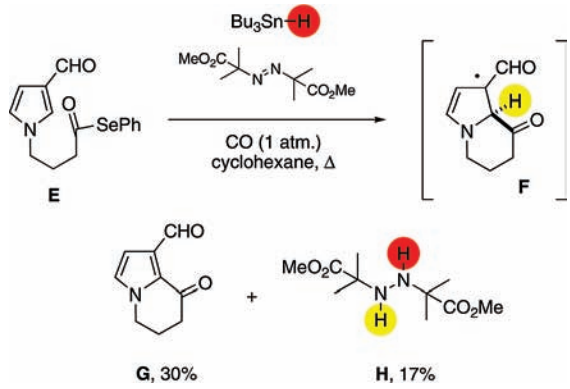
(10) For a review, see: (a) Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794–802. For representative reports: (b) Guin, J.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 779–782. (c) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726–5733. (d) Baguley, P. A.; Binmore, G.; Milne, A.; Walton, J. C. *Chem. Comm.* **1996**, 2199–2200. (e) ref 8f.

(11) Hermecz, I.; Vasvari-Debreczy, L.; Horvath, A.; Balogh, M.; Kokosi, J.; De Vos, C.; Rodriguez, L. *J. Med. Chem.* **1987**, *30*, 1543–1549.

(12) For arguments in favor of a rearomatization step involving a H-abstraction mechanism by AIBN, see: (a) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343–7366. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377–1393. (c) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed* **2004**, *43*, 95–98. When aryl iodides are involved in intramolecular radical additions to quinolines, a SET process may operate and only a catalytic amount of AIBN is required. See: (d) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387–3400. (e) Harrowven, D. C.; Guy, I. L.; Nanson, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 2242–2245. See also: (f) Bowma, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119–10128. Oxygen can also be responsible for the aromatization. See: (g) Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706–13707.

(13) (a) Allin, S. M.; Barton, W. R. S.; Russell Bowman, W.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887–7890. (b) Allin, S. M.; Barton, W. R. S.; Russell Bowman, W.; Bridge (née Mann), E.; Elsegood, M. R. J.; McInally, T.; McKee, V. *Tetrahedron* **2008**, *64*, 7745–7758.

Scheme 3. Evidence for H• Trapping in the Literature[a]



[a] See ref 13.

of AIBN employed slightly eroded the efficiency of the reaction. The NMR yields of **4** decreased from 79% to 72%, 64%, and 57% when the loading was decreased from 1.5 equiv to 1, 0.5, and 0.25 equiv (entries 3−6). Below 1 equiv, some byproducts arising from reduction without cyclization (**5**, 8%) as well as some starting material (6%) were isolated.

3. Mechanistic Considerations

When cyanamide **3** was treated with tributyltin deuteride, quinazolinone **7** was isolated in 55% yield with 83% deuterium incorporation, as measured by ^{1}H NMR (Scheme 4), along with a minor amount of *exo*-methylene compound **8** (i.e., the product expected from the aborted cascade). The deuterium is on the five-membered ring. On the other hand, pentadeuterated cyanamide **9** led to quinazolinone **10** (48% yield in benzene, 59% in *t*-butanol), where the deuterium is on the methyl group (>95% deuterium incorporation measured by MS).

Those labeling experiments thus confirmed that the reduction of the double bond proceeds via migration of a hydrogen atom from the benzoyl group to the exo methylene moiety, followed by radical termination by transfer of a second hydrogen from the mediator (Scheme 5). This key hydrogen transfer is reminiscent of the Mayo mechanism of initiation in the thermal polymerization of styrene.[14]

Following the formation of intermediate cyclohexadienyl radical **11**,[8] there are three distinct possibilities for the migration to take place (Scheme 6). The hydrogen atom can migrate in an intramolecular fashion (path A). It can β-eliminate from **11**, and subsequently re-add at the exomethylenic carbon of **8** (path B).[15] The transfer can occur in a bimolecular fashion. In this latter scenario, some **8** would initially be formed from a transfer of H• from **11** to AIBN. Then, **8** would abstract an H• from **11** thus leading to final radical **12** and another molecule of **8** (path C).

In order to sort between path A and B/C, we carried out double labeling experiments. Cyanamides **9** (pentadeuterated) and **13** (*p*-methoxy) were chosen as substrates for this purpose. Treated under the optimized cascade conditions devised previously, cyanamide **13** led to the expected product **14** in 72% yield in refluxing *t*-butanol (Scheme 7).

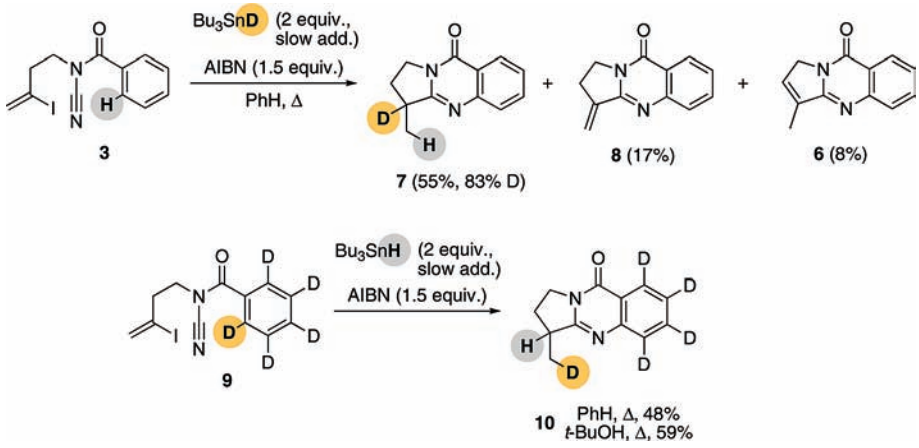
We next carried out the reaction with half an equivalent each of **9** and **13**. If the migration had been fully intramolecular (path A), then **9** should have led to **10** only via deuterium migration, whereas **13** would have yielded **14**, as before. Thus an equimolar mixture of **10** and **14** would have been expected. On the other hand, if the reaction followed paths B or C, then one would have expected exchange, and the formation of **15** and **16**.

In the event, an equimolar mixture of the four possible compounds was isolated (Scheme 8). Consequently, path A could be excluded, but we could not discriminate between the two remaining paths at that stage.

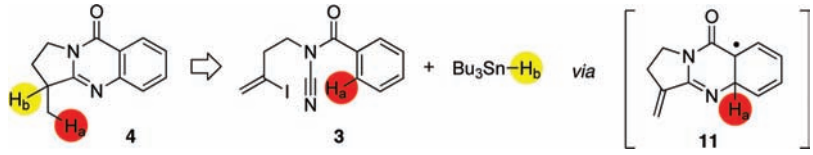
4. Interrupted Cascades

As mentioned earlier, the final reduction of the exomethylene compound would arise from trapping of H• by a molecule of **8** formed in the early stages of the reaction. We imagined that the bimolecular approach required in path C would be more

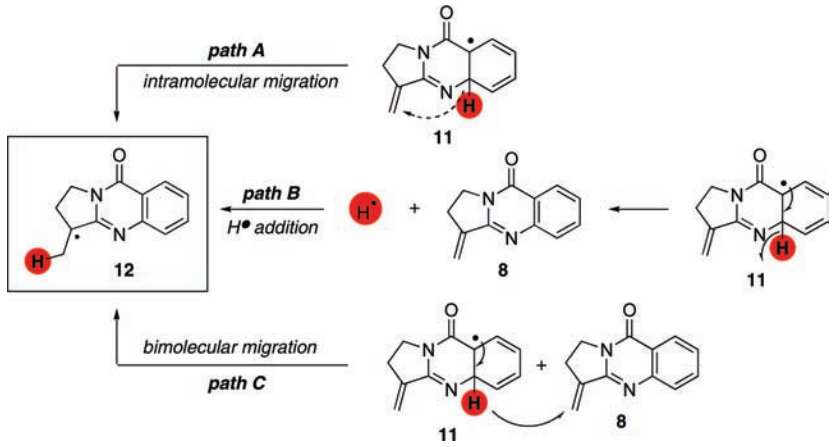
Scheme 4. Labeling Experiments for the Migration of H•



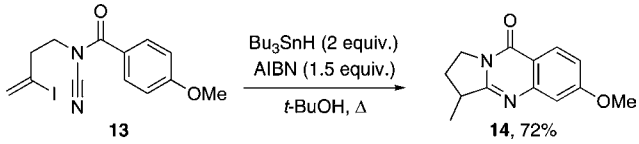
Scheme 5. Origin of the Two Hydrogens in Quinazolinone **4**



Scheme 6. Possible Mechanisms for the H• Migration



Scheme 7. Modification of the Aromatic Ring



sensitive to steric hindrance than the addition of a putative H• to the double bond (path B).

When an additional methyl substituent was installed onto the double bond, the efficiency dropped sharply since only 27% of the reduced **18** was isolated (Scheme 9). The major product was the aborted adduct **19** (58%, 5:1 ds). Similarly, substrate **20** led to **6** in 82% yield.

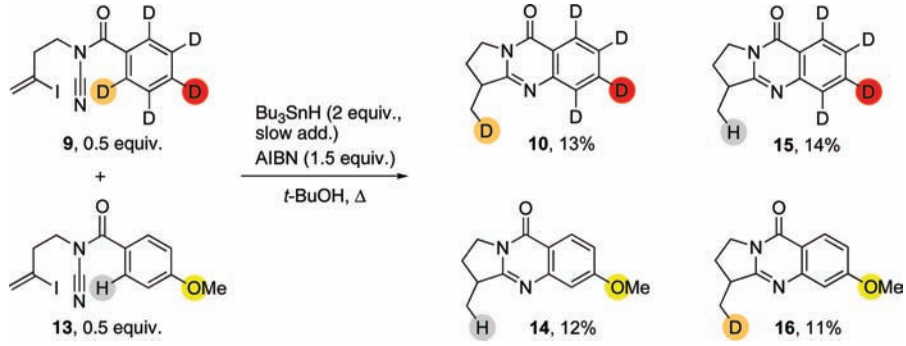
Since steric hindrance in those two cases should not be a preponderant factor for the radical addition of hydrogen atoms, we believe this suggests that path C is the operating mechanism for the final migration (see below).

From a synthetic point of view, these results suggested that the cascade could be stopped en route to the final product. With a view of developing conditions to control it toward either one or the other outcome, we endeavored to devise modifications in our reaction that would deliver cleanly the unsaturated product coming from the interrupted process.

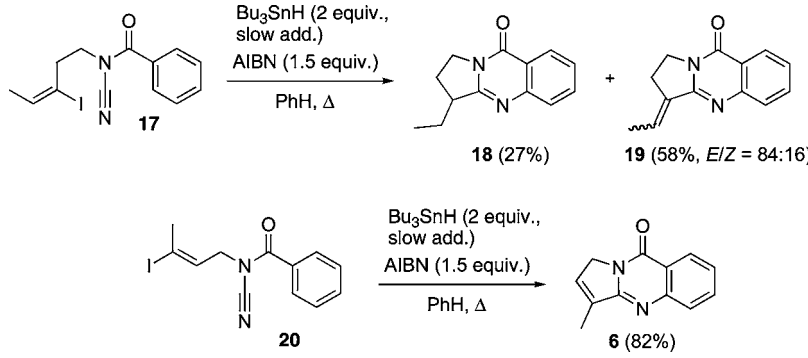
Introduction of substituents in the meta position of the benzoyl groups, that is ortho to the carbon undergoing addition seemed a potential way of again blocking the bimolecular approach, this time from the aromatic region of the substrates.

Additional methyl substituents had no effect, since 63% of reduced **22** were obtained from **21**, along with the usual migration product **23**. Introduction of *t*-butyl groups proved highly detrimental (Scheme 10). Only 33% of reduced **25** was isolated from **24**. Because the overall yield is low, it is not possible to conclude whether steric hindrance on the aromatic ring blocked the final reduction or not.

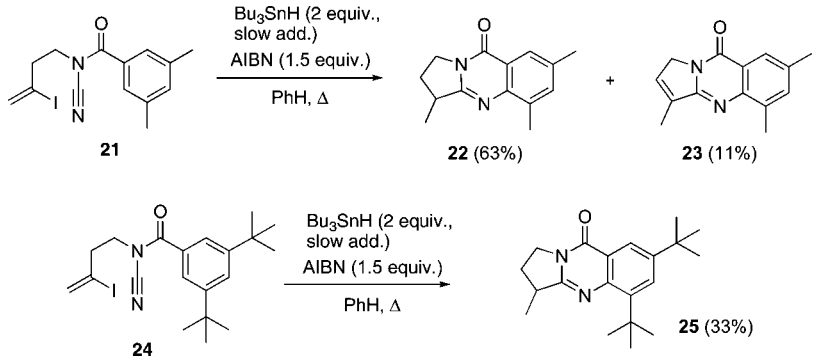
Scheme 8. Double-Labeling Experiment



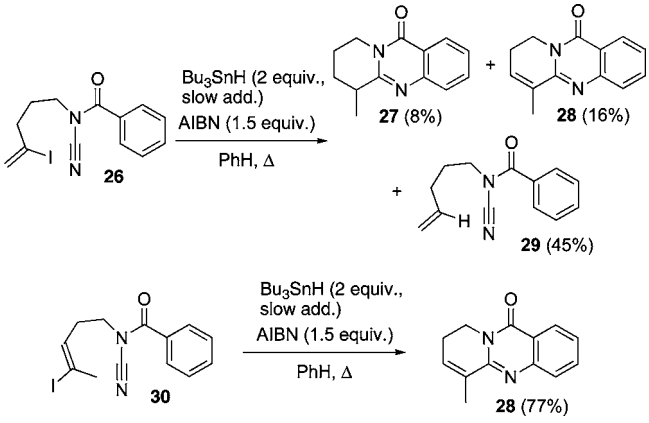
Scheme 9. Influence of the Steric Hindrance



Scheme 10. Steric Hindrance on the Aromatic Ring



Scheme 11. Influence of the Ring Size



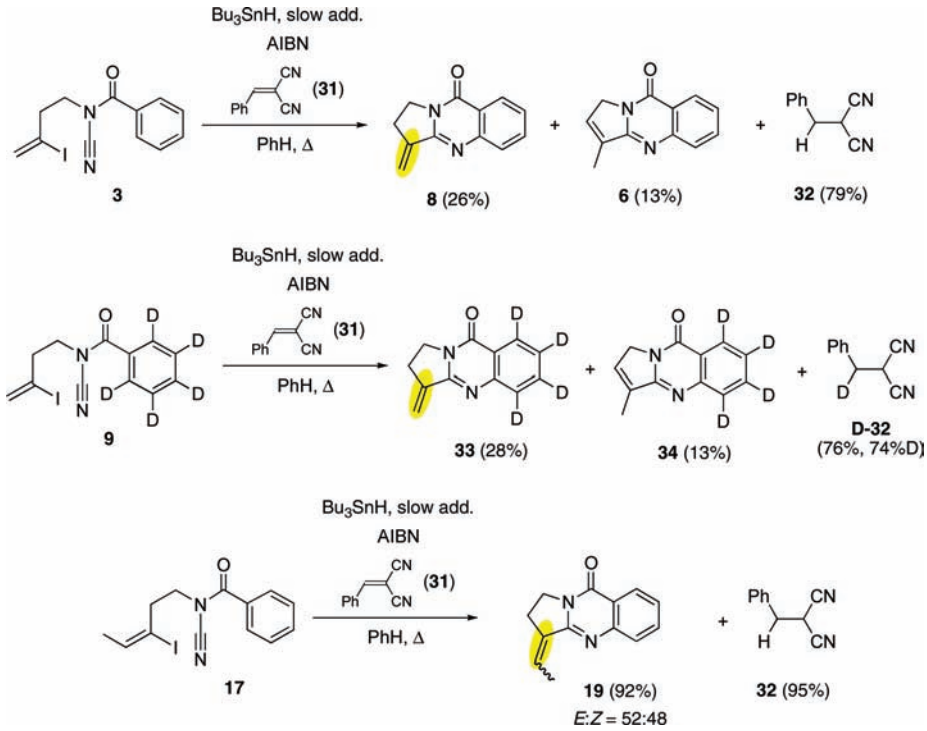
The initial cyclization featured a 5-*exo-dig* closure eventually leading to 5−6−6 tricyclic systems. We decided to extend our investigations to the homologous 6−6−6 system, with an initial 6-*exo-dig* cyclization. Reaction of **26** delivered mostly dehalogenated cyanamide **29** (45%, Scheme 11). The two expected cyclized products were also isolated (24% overall), albeit the aborted cascade was predominant in this case (2:1). The low efficiciency of the cascade is consistent with a slower 6-*exo-dig* cyclization, although we were surprised by the intensity of the rate reduction. Also, the increased amount of "interrupted" product **28** may come from a more rapid migration of the double bond to the *endo* position relative to the 5−6−6 series.

By switching the position of the double bond in starting cyanamide **30**, we could again take advantage of the blocking of the final migration to obtain a good yield of **28** (77%).

Competition experiments were next devised with a view of rerouting the hydrogen transfer toward a sacrificial acceptor. In this way, the final transfer would be aborted, delivering the unsaturated products. Benzylidenemalonodinitrile (**31**) was chosen as the sacrificial acceptor.

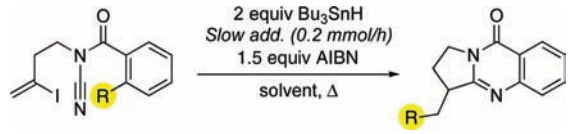
Reaction of **3** in the presence of 5 equiv of the dinitrile **31** resulted in a complete suppression of the reduced product and provided instead adduct **32** (Scheme 12). However, the resulting exomethylene product **8** was not very stable under the reaction

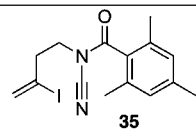
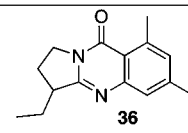
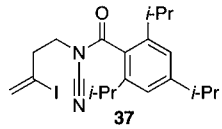
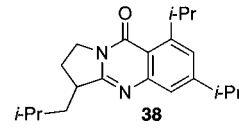
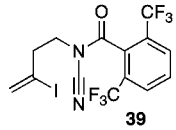
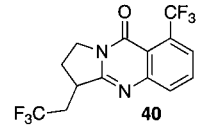
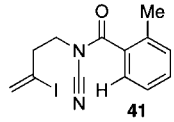
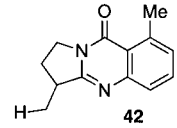
Scheme 12. Use of a Sacrificial H• Acceptor[a]



[a] Conditions: Bu_3SnH (2 equiv) and AIBN (1.5 equiv).

Table 2. Radical Migration of Alkyl Substituents



Entry	Substrate	Solvent	Product	Isolated yield (%)
1	 **35**	PhH	 **36**	45
2	**35**	*t*-BuOH	**36**	47
3	 **37**	PhH	 **38**	52
4	 **39**	PhH	 **40**	24[a]
5	**39**	*t*-BuOH	**40**	55[a]
6	 **41**	PhH	 **42**	58
7	**41**	*t*-BuOH	**42**	69

[a] Very slow addition (0.06 mmol/h) of Bu_3SnH is required to avoid decomposition.

conditions; thus, the isolated yield was disappointing. The outcome with the pentadeuterated derivative **9** was very similar, furnishing D-**32**. Yet, no significant rate change was observed. This likely indicates that the reduction is not the kinetically determinant step of the cascade, which is probably the radical addition to the aromatic moiety.

To our pleasure, the cyclization of **17** delivered **19** in 92% yield (approximately 1:1 mixture of olefin isomers). The selectivity was much improved under the "aborted" conditions, since there was no trace of **18** (27% under the normal conditions).

5. Carbon-Substituent Migrations

With the migration of hydrogen atoms in hand, we approached the more synthetically useful migration of alkyl substituents. We first investigated *ortho*,*ortho*′-disubstituted benzoyl cyanamides (Table 2).

To our delight, the title cascades were successful. In a typical experiment, a methyl group underwent the migration in refluxing benzene upon slow addition of TBTH in the presence of AIBN (45%, Table 2, entry 1).[16] *t*-BuOH only led to a slight increase in yield (entry 2). Other alkyl radicals (e.g., isopropyl) also were conducive to the migration (entry 3).

The most promising outcome was provided by the migration of the trifluoromethyl radical, which was obtained in 55% yield overall (entry 5), albeit in that case the reaction in benzene was much less efficient (24%, entry 4).[17] Given the number of fluorine-containing molecules, especially with CF_3 substitution, and nitrogen heterocycles in active pharmaceutical ingredients, this entry into variously substituted fluorine-containing aromatic heterocycles should be of particular importance for medicinal chemists.[18]

Lastly, we ran a competition experiment between hydrogen atom and alkyl group migration (entries 6 and 7). As was

(14) (a) Mayo, F. R. *J. Am. Chem. Soc.* **1968**, *90*, 1289–1295. (b) Chong, Y. K.; Rizzardo, E.; Solomon, D. H. *J. Am. Chem. Soc.* **1983**, *105*, 7761–7762.

(15) As proposed by one referee, AIBN could also serve as relay for hydrogen delivery, through the intervention of H-AIBN adduct (see ref 13).

(16) As pointed out by one referee, the addition of a methyl radical on a simple alkene is slow and propagation of the radical chain would not be operative (see for these kinetics: Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1996**, *118*, 437–439). However, we can anticipate that **8** due to its highly conjugated character is a good acceptor of alkyl radicals.

(17) A possible side reaction can be the CF_3 radical addition on benzene: (a) Stefani, A. P.; Szwarc, M. *J. Am. Chem. Soc.* **1962**, *84*, 3661–3666. (b) Whittemore, I. M.; Stefani, A. P.; Szwarc, M. *J. Am. Chem. Soc.* **1962**, *84*, 3799–3803.

anticipated, the reaction of cyanamide **41** led to the unique formation of reduced **42** (58% in benzene, 69% in *t*-BuOH). This can be explained by the more rapid radical addition at the less substituted carbon atom of the aromatic ring.

6. Conclusion

We have designed a novel radical cascade involving *N*-acyl cyanamides. Heteroaromatic structures can be accessed via a domino process that builds up to two C−C and one C−N bonds. The central feature of the reaction is the radical migration of hydrogen atoms or carbon substituents triggered by rearomatization of a cyclohexadienyl radical generated by radical addition to the aromatic ring. To our knowledge this is unprecedented in a context of radical cascades and should be of use to the broad community of synthetic as well as medicinal chemists.

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Supporting Information Available: Procedures and characterization of all new compounds (including copies of the NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

JA910653K

(18) (a) Dolbier, W. R., Jr. *J. Fluor. Chem* **2005**, *126*, 157–163. (b) Bégué, J. P.; Bonnet-Delpon, D. *J. Fluor. Chem.* **2006**, *127*, 992–1012. (c) Kirk, K. L. *J. Fluor. Chem.* **2006**, *127*, 1013–1029. (d) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891–897.