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Catalytic Asymmetric Synthesis of Diazabicyclo[3.1.0]hexanes by 1,3-Dipolar Cycloaddition of Azomethine Ylides with Azirines.

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Substituted 1,3-diazabicyclo[3.1.0]hexanes with two contiguous quaternary stereocentres are readily prepared by catalytic asymmetric [3+2] cycloaddition of α-substituted iminoesters with azirines. High diastereoselectivities and enantioselectivities (up to 98% *ee*) are achieved using Cu^{I}/(*R*)-Fesulphos as catalytic system.

Aziridine alkaloids are highly valuable heterocyclic compounds extensively used as synthetic intermediates.[1] In addition, this structural fragment is present in a variety of drugs and biologically active natural products.[2] Specifically, the diazabicyclo[3.1.0]hexane scaffold is found in several compounds with interesting biological properties such as Mitomycins[3] (antibiotic, antitumor), Albomitomycin C[4] (neoplasm inhibitor) or Imexon[5] (immunosuppressant, Figure 1). However, the existing methodologies for the enantioselective preparation of aziridinoimidazolines are cumbersome and usually require multistep sequences starting from enantioenriched materials.[6]

The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides is arguably one of the most efficient and atom economic procedures for the enantioselective preparation of pyrrolidine type heterocycles.[7] In the last two decades a great effort has been made to expand the scope of this reaction to a variety of dipolarophile and azomethine partners.[8] As a result, the cycloaddition between iminoesters and activated olefins has witnessed an astonishing progress in enantioselective pyrrolidine synthesis.[9] In this context, we and others have recently demonstrated that taking advantage of the strain ring release during the [3+2] cycloaddition, sterically hindered strained dipolarophiles, such as trisubstituted cyclobutenones[10] or cyclopropenes,[11] are suitable substrates in this reaction.

In contrast, the use of imines as heterodipolarophiles, leading to the formation of imidazolines, has been much less studied. These scarce reports on catalytic asymmetric azomethine ylide-imine cycloaddition typically involve aldehyde derived imines (Scheme 1).[12]

We envisaged that by strain release sterically hindered azirines could participate as dipolarophiles in this transformation paving the way to the preparation of enantioenriched diazabicyclo[3.1.0]hexane analogues with potential biological interest (Scheme 1). However, these three membered azaheterocycles have been barely used as dipolarophiles in 1,3-dipolar cycloadditions[13] and, as far as we are aware, there are no reported examples of their use in catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides.

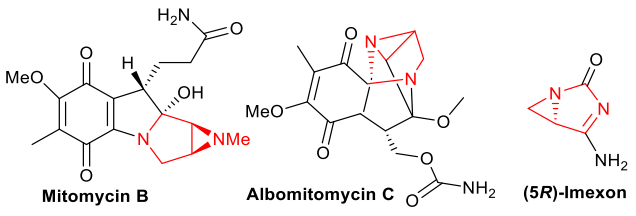
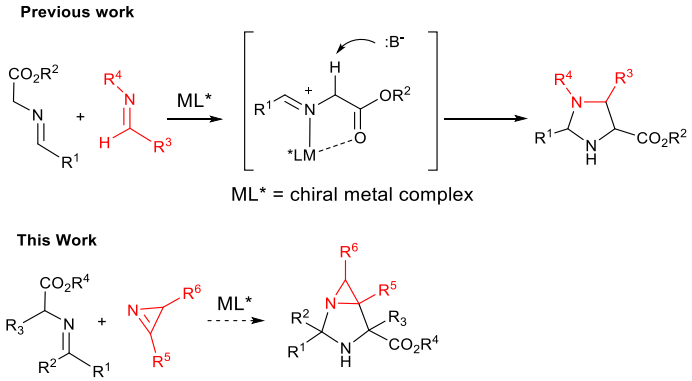


Figure 1: Biologically active aziridinopyrrolidines



Scheme 1: Imines in catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides

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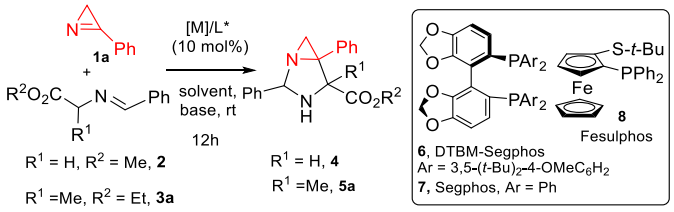
In order to test the feasibility of azirines as dipolarophiles in the 1,3-dipolar cycloaddition of azomethine ylides, 3-phenyl-2H-azirine **1a** and glycine derived iminoester **2** were chosen as model substrates. Under conditions commonly used by our research group with other dipolarophiles ($Cu(CH_3CN)_4$ as metal source, DTBM-Segphos (**6**) as ligand, and KO^{t}Bu as base in THF)[14] the expected cycloadduct **4** was obtained with high conversion and excellent diastereocontrol (only the *endo* isomer was observed by ^{1}H-NMR, Table 1, entry 1). However, the standard silica gel chromatography purification of the product led to the formation of two diastereoisomers by silica gel promoted epimerization of the aminal chiral centre.[15] When the purification was performed by chromatography on Et_3N deactivated silica, the diazabicycle **4** could be isolated as a single diastereomer with moderate yield and low enantioselectivity (20% *ee*, entry 1). Other metal sources, chiral ligands, bases or solvents did not improve the initial results (entries 2-5). To try to improve the chemical stability of the adducts we next evaluated the cycloaddition of the alanine derived iminoester **3a**, which would lead to the formation of a diazabicycle with a quaternary stereocentre at C-4 (**5a**). Pleasingly, with DTBM-Segphos (**6**) as ligand, KO^{t}Bu as base in CH_2Cl_2, the reaction took place with similar yield (46%), excellent *endo*-diastereoselectivity and improved enantiocontrol (**5a**, 68% *ee*, entry 6). Similar results were obtained with the less bulky Segphos ligand **7** (entry 7). Interestingly, very high enantioselectivity was achieved in the presence of (*R*)-Fesulphos ligand **8** (76%, 95% *ee*, entry 8). Disappointingly, a significant drop in conversion and asymmetric induction was observed when the catalyst loading was reduced to 5 mol% (entry 9).

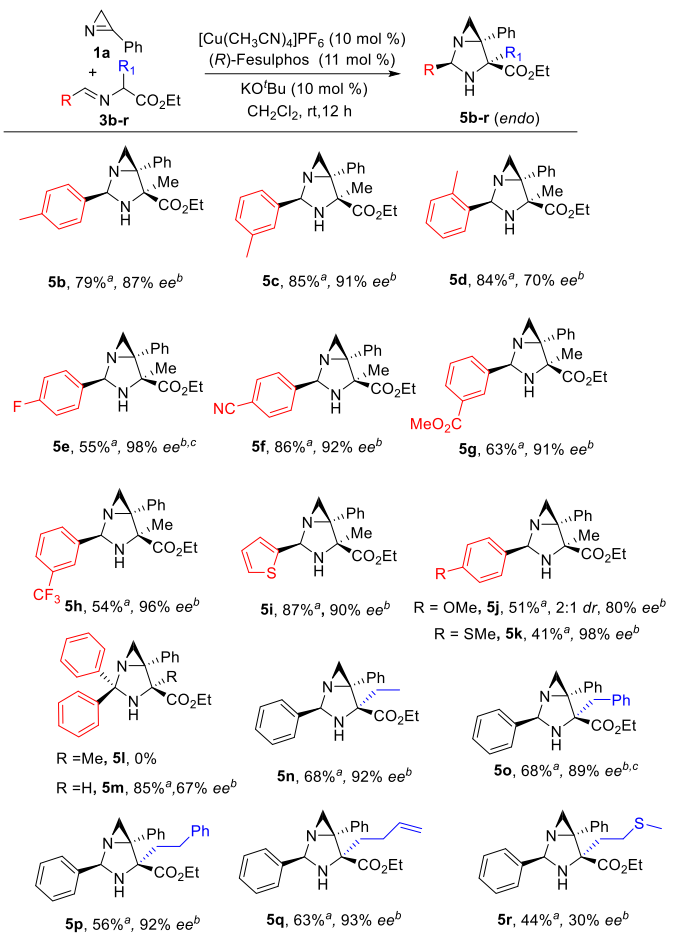
Table 1: Optimization of the reaction conditions



Entry	R^1	[M]	L*	base	solvent	yield(%)[b]	*ee* (%)
1	H	$CuPF_6$[a]	**6**	KO^{t}Bu	THF	52	20
2	H	$CuPF_6$[a]	**6**	KO^{t}Bu	CH_2Cl_2	54	24
3	H	$CuPF_6$[a]	**6**	Et_3N	CH_2Cl_2	--	--
4	H	AgOAc	**6**	KO^{t}Bu	CH_2Cl_2	10	--
5	H	$CuPF_6$[a]	**8**	KO^{t}Bu	CH_2Cl_2	65	24
6	Me	$CuPF_6$[a]	**6**	KO^{t}Bu	CH_2Cl_2	46	68
7	Me	$CuPF_6$[a]	**7**	KO^{t}Bu	CH_2Cl_2	34	69
8	Me	$CuPF_6$[a]	**8**	KO^{t}Bu	CH_2Cl_2	76	95
9 [d]	Me	$CuPF_6$[a]	**8**	KO^{t}Bu	CH_2Cl_2	58	79

[a]$Cu(CH_3CN)_4PF_6$. [b]Isolated yield after chromatographic purification. [c]*ee* determined by HPLC. [d]5 mol% of catalyst.

Table 2: Scope regarding the substitution at the iminoester



[a]Isolated yield after chromatographic purification. [b]*ee* determined by HPLC. [c]The reaction was carried out at -20°C.

With these optimized reaction conditions in hand, we next investigated the scope of the 1,3-dipolar cycloaddition with regard to the substitution at the azomethine ylide. As depicted in Table 2, different aromatic alanine derived iminoesters were initially investigated. The reaction of *meta* or *para* substituted iminoesters resulted in good yields, almost complete *endo*-diastereoselectivity and high enantioselectivity (adducts **5b** and **5c**), while a lower enantioselectivity was obtained from an *ortho*-substituted substrate (product **5d**, 70% *ee*). Electron deficient aromatic iminoesters, bearing fluoro (**3e**), cyano (**3f**), ester (**3g**) or trifluoromethyl (**3h**) groups, as well as the thienyl iminoester **3i**, proved also to be excellent substrates in this transformation (90-98% *ee*). The reaction of aryl iminoesters **3j** and **3k** having stronger electron-donating groups such as OMe and SMe afforded the corresponding adducts **5j** and **5k** in moderate yields and good enantioselectivities, although a 2:1 mixture of diastereoisomers was obtained using the *para*-anisaldehyde derivative **3j** (adduct **5j**).

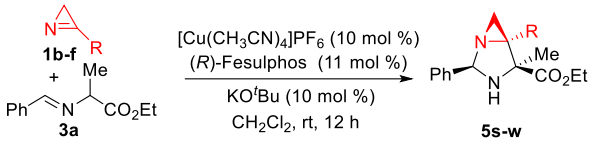
Not unexpectedly no cycloaddition was observed with the highly sterically demanding benzophenone-derived alanine ketimine ester **3l**. In contrast, the reaction with the less bulky glycine analogue **3m** afforded the adduct **5m,** having a

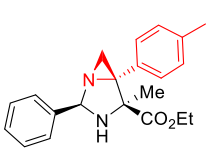
quaternary stereocentre at C-2, with moderate enantioselectivity (67% *ee*).

To extend the scope of this cycloaddition, the effect of the substitution at the alpha position of the iminoester was also investigated. Schiff bases prepared from other amino esters such as ethyl aminobutanoate (**3n**), ethyl phenylalaninate (**3o**), ethyl amino-4-phenylbutanoate (**3p**) or the imino ester **3q** bearing an alkenyl substituent worked well (adducts **5n-5q**, 89%-93% *ee*). In contrast, the methionine ethyl ester derivative afforded a poor enantioselectivity (**5r,** 30% *ee*).

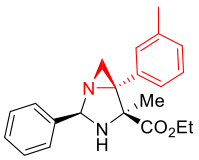
The scope of the reaction regarding the substitution at the azirine partner is summarized in Table 3. Under the optimized reaction conditions the reaction proceeded smoothly with 2-arylazirines regardless of the para or meta position of the methyl substituent (Table 3, substrates **5s** and **5t**). Substrates bearing halogen substituents (**1u** and **1v**) led to the corresponding diazabicycles with good yield (82-84%) and excellent enantioselectivities (92-97% *ee*). However, a lower reactivity albeit similar enantioselectivity was observed with 2-arylazirines bearing strong electron donating substituents, (**5w**, 35%, 90% *ee*).

Table 3: Scope regarding

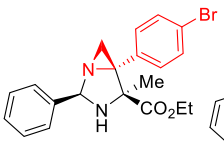




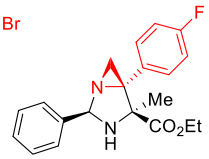
5s, 95%[a], 99% *ee*[b]



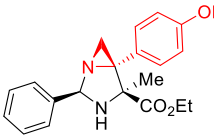
5t, 77%[a], 91% *ee*[b]



5u, 82%[a], 97% *ee*[b]



5v, 84%[a], 92% *ee*[b]

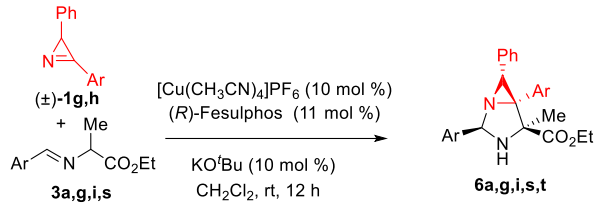


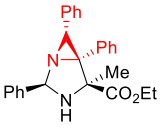
5w, 35%[a], 90% *ee*[b]

[a]Isolated yield after chromatographic purification. [b]*ee* determined by HPLC.

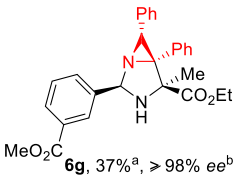
Next, we set out to study the behaviour of racemic 2,3-disubstituted azirines in this cycloaddition (Table 4). Thus, the reaction of diphenylazirine **1g** with alanine derived iminoester **3a** afforded a single adduct **6a** with 37% yield and excellent enantioselectivity (98% *ee*). This outcome strongly suggests that an efficient kinetic resolution process has took place. Disappointingly, the unreacted azirine could not be recovered, likely due to its instability. Next, a variety of disubstituted racemic azirines were tested in the cycloaddition affording similarly a single adduct bearing four stereocentres with moderate to excellent *ee´s* (Table 4, adducts **6g**, **6i**, **6s** and **6t**).

Table 4: Cycloaddition of racemic diarylazirines **1g** and **1h**

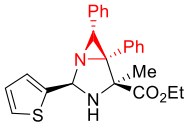




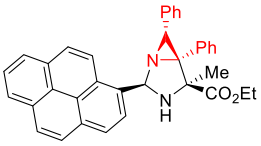
6a, 37%[a], 97% *ee*[b]



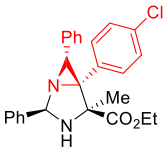
6g, 37%[a], ⩾ 98% *ee*[b]



6i, 29%[a], 71% *ee*[b]



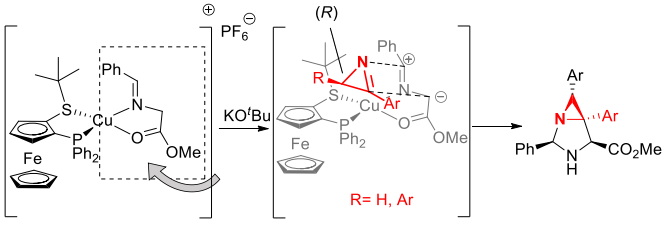
6s, 45%[a], 93% *ee*[b]



6t, 39%[a], 53% *ee*[b]

[a]Isolated yield after chromatographic purification. [b]*ee* determined by HPLC.

The relative configuration of diazabicycles **5** and **6** was unambiguously determined by X-ray diffraction of racemic **5r** and **6s**.[16] The absolute configuration of the diazabicycles was tentatively established based on the model previously reported by us for Cu^{I}/(*R*)-Fesulphos catalysed cycloadditions[17] and confirmed by comparison of experimentally measured and simulated by DFT circular dichroism of (+)-**6s** (see ESI for details). Thus, according to this model the approach of the azirine would occur by the less hindered face of the key chiral metallodipole, avoiding the steric interaction with the bulky ^{t}Bu group of the P,S-ligand (Scheme 2). Accordingly, the 2,3-disubstituted azirines of (*R*) configuration would react at a faster rate than the (*S*) enantiomers avoiding the steric interaction between the azirine substituent and the ^{t}Bu group of the copper catalyst (Scheme 2).



Scheme 2: Proposed stereochemical model.

In conclusion, we have developed a practical copper catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with azirines. The use of Cu^{I}/(*R*)-Fesulphos as catalyst allows the

preparation of diazabicyclo[3.1.0]hexanes bearing up to four stereocentres with almost complete *endo*-diastereoselectivity and excellent enantioselectivities.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 J.B. Sweeney, *Chem. Soc. Rev*., 2002, **31**, 247
2 F. M. D. Ismail, D. O. Levitsky and V. M. Dembitsky, *Eur. J. Med. Chem.*, 2009, **44**, 3373.
3 (a) M. Varoglu, Y. Mao and D. H. Sherman, *J. Am. Chem. Soc.*, 2001, **123**, 6712; (b) V.N. Iyer and W. Szybalski, *Science*, 1964, **145**, 55.
4 M. Kono, Y. Saitoh, K. Shirahata, Y. Arai and S. Ishii, *J. Am. Chem. Soc.*, 1987, **109**, 7224.
5 K. Dvorakova, C. M. Payne, M. E. Tome, M. M. Briehl, T. McClure and R. T. Dorr, *Biochem. Pharm.*, 2000, **60**, 749.
6 (a) J. E. Rodríguez-Borges, M. L. C. Vale, F. R. Aguiar, M. J. Alves and X. García-Mera, *Synthesis*, 2008, 971; (b) C. J. Andres and A. I. Meyers, *Tetrahedron Lett*., 1995, **36**, 3491.
7 For the interest of pyrrolidines in synthetic and medicinal chemistry, see: (a) M. Kuhnert, A. Blum, H. Steuber and W. E. Diederich, *J. Med. Chem.*, 2015, **58**, 4845; (b) R. D. Taylor, M. MacCoss and A. D. G Lawson. *J. Med. Chem.*, 2014, **57**, 5845; (c) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451; (d) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139; (e) J. W. Daly, T. F. Spande and H. M. Garraffo, *J. Nat. Prod*., 2005, **68**, 1556; (f) S. G. Pyne, A. S. Davis, N. J. Gates, K. B. Lindsay, T. Machan and M. Tang, *Synlett*, 2004, 2670.
8 For recent reviews, see: (a) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2019, **55**, 11979; (b) I. Arrastia, A. Arrieta and F. P. Cossio, *Eur. J. Org. Chem.*, 2018, **43**, 5889; (c) X. Fang and C.-J. Wang, *Org. Biomol. Chem*., 2018, **16**, 2591; (d) B. Bdiri, B.-J. Zhao and Z.-M. Zhou, *Tetrahedron: Asymmetry*, 2017, **28**, 876; (e) H. A. Döndas, M. G. Retamosa and J.M. Sansano, *Synthesis*, 2017, **49**, 12434; (f) T. Hashimoto and K. Maruoka, *Chem. Rev.,* 2015, **115**, 5366; (g) J. Adrio and J. C. Carretero, *Chem. Commun*., 2014, **50**, 12434; (h) C. Nájera, and J. M. Sansano, *J. Organomet. Chem*., 2014, 771; (i) Y. Xing and N.-X. Wang, *Coord. Chem. Rev*., 2012, **256**, 938; (j) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2011, **47**, 67834.
9 For very recent references, see: (a) Y.-P. Zhang, Y. You, J.-Q. Zhao, X.-J. Zhou, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *Org. Chem. Front.,* 2019, **6**, 1879; (b) G. S. Caleffi, O. Larrañaga, M. Ferrádiz-Saperas, P. R. R. Costa, C. Nájera, A. de Cózar, F. P. Cossío and J. M. Sansano, *J. Org. Chem.* 2019, **84**, 10593; (c) F. Cheng, S. J. Kalita, Z.-N. Zhao, X. Yang, Y. Zhao, U. Schneider, N. Shibata and Y. Y. Huang, *Angew. Chem. Int. Ed*., 2019, **58**, 16637; (d) B. Liu, W. Li, H.-H. Wu and J. Zhang, *Org. Chem. Front.*, 2019, **6**, 694; (e) R. Chowdhury, A. K. Dubey and S. K.Ghosh, *J. Org. Chem*., 2019, **84**. 2404; (f) X. Chang, S. Xi-Shang, C. Che, Y.-Z. Hu, H.-Y. Tao and C.-J. Wang, *Org. Lett*., 2019, **21**, 1191; (g) C. Shen, Y. Yang, L. Wei, W.-W. Dong, L. W. Chung and C.-J. Wang, *iScience*, 2019, **11**, 146; (h) Y. Wu, B. Xu, B. Liu, Z.-M. Zhang and Y. Liu, *Org. Biomol. Chem*., 2019, **17**, 1395. (i) L. Liang, H.-Y. Niu, D.-C. Wang, X.-H. Yang, G.-R. Qu and H.-M. Guo, *Chem. Commun.*, 2019, **55**, 553; (j)Y. Xiong, Z. Du, H. Chen, Q. Tan, C. Zhang, L. Zhu, Y. Lan and M. Zhang, *J. Am. Chem. Soc.*, 2019, **141**, 961.
10 J. Corpas, A. Ponce, J. Adrio, and J. C. Carretero, *Org. Lett.,* 2018, **20**, 3179.
11 (a) H. Deng, W.-L. Yang, F. Tian, W. Tang and W.-P. Deng, *Org. Lett*., 2018, **20**, 4121; (b) Y. Yuan, Z.-J, Zheng, F. Ye, J.-H. Ma, Z. Xu, X.-F. Bai, L. Li and L.-W. Xu, *Org. Chem. Front.*, 2018, **5**, 2759.
12 (a) L. Wei, Q.-H. Li, and C.-J. Wang, *J. Org. Chem.,* 2018, **83**, 11814; (b) B. Yu, K.-F. Yang, X.-F. Bai, J. Cao, Z.-J. Zheng, Y.-M. Cui, Z. Xu, L.; Li and L.-W. Xu, *Org. Lett.*, 2018, **20**, 2551; (c) B. Yu, X.-F. Bai, J.-Y. Lv, Y. Yuan, J. Cao, Z.-J. Zheng, Z. Xu, Y.-M. Cui, K.-F. Yang and L.-W. Xu, *Adv. Synth. Catal*. 2017, **359**, 3577; (d) Y.-M. Wang, H.-H. Zhang, C. Li, T. Fan and F. Shi, *Chem. Commun.*, 2016, **52**, 1804; (e) W.-J. Liu, X.-H. Chen and L.-Z. Gong, *Org. Lett.,* 2008, **10**, 5357; (f) Q.-H. Li, L. Wei, X. Chen and C.-J. Wang, *Chem. Comm un*., 2013, **49**, 6277.
13 For the use of azirines in non-asymmetric 1,3-dipolar cycloadditions with azomethine ylides, see: (a) A. Angyal, A. Demjén, V. Harmat, J. Wölfling, L. G. Puskás, and I. Kanizsai, *J. Org. Chem*., 2019, **84**, 4273; (b) S. Borra, D. Chandrasekhar, S. Adhikary, S. Rasala, S. Gokulnath, and R. A. Maurya *J. Org. Chem.,* 2017, **82**, 2249. For selected examples with other dipoles, see: (c) Y. Wu, B. Tian, C. Hu, K. Sekine, M. Rudolph, F. Romingera and A. S. K. Hashmi, *Org. Biomol. Chem.,* 2019, **17**, 5505; (d) Y. Baek, C. Maeng, H. Kim, and P. H. Lee, *J. Org. Chem*., 2018, **83**, 2349; (e) J. E. Curiel Tejeda, L. C. Irwin, and M. A. Kerr *Org. Lett.*, 2016, **18**, 4738;
14 a) A. Pascual-Escudero, A. de Cózar, F. P. Cossío, J. Adrio, and J. C. Carretero, *Angew. Chem. Int. Ed.*, 2016, **55**, 15334; (b) E. M. Arpa, M. Gónzalez-Esguevillas, A. Pascual-Escudero, J. Adrio and J. C. Carretero, *J. Org. Chem.* 2016, **81**, 6128; (c) A. Pascual-Escudero, J. Adrio and J. C. Carretero, *Chem. Eur. J.* 2015, **21**, 4561.
15 See Supporting Information for detalis.
16 CCDC 1934764 (**5r**) and CCDC 1934765 (**6s**) contains the supplementary crystallographic data for this paper. www.ccdc.cam.ac.uk/data_request/cif.
17 (a) S. Cabrera, R. Gómez Arrayás, B. Martín-Matute, F. P. Cossío and J. C. Carretero, *Tetrahedron* **2007**, *63*, 6585; (b) See also reference 10.

