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Divergent Chemo-, Regio-, and Diastereoselective Normal Electron-Demand Povarov-Type Reactions with α-Oxo-ketene Dienophiles

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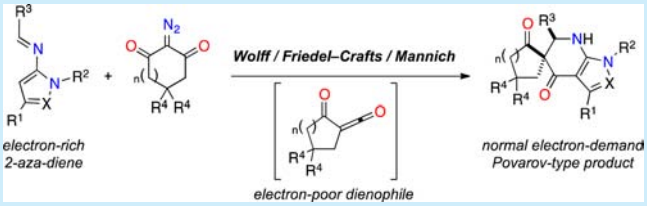
Supporting Information

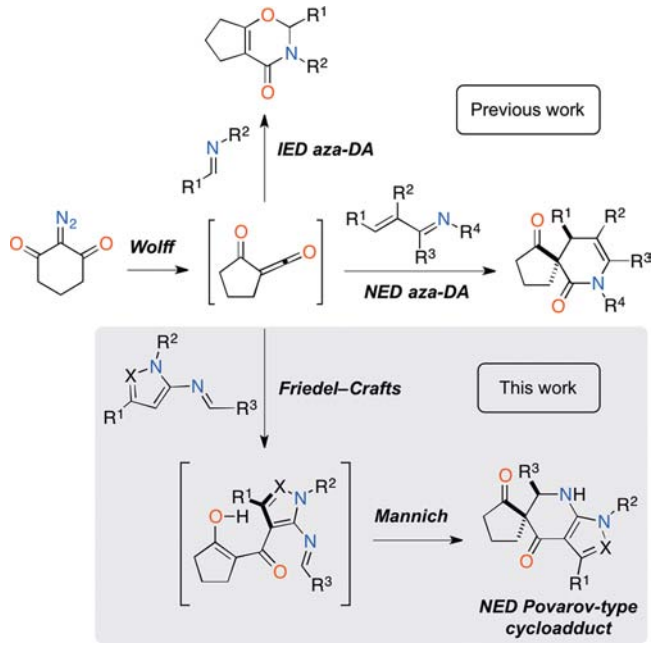
ABSTRACT: The reactions between electron-rich 2-aza-dienes and α-oxo-ketenes derived from the Wolff rearrangement of 2-diazocycloalkane-1,3-diones chemo- and regioselectively produced spiro hydropyrid-4-ones with good to excellent diastereoselectivities. These reactions are likely to proceed via a domino Wolff/Friedel–Crafts/intramolecular Mannich process. Prolonged domino sequences also allowed the expeditious preparation of a series of pyrazolopyridine and pyridopyrimidine heterocycles.



The stereocontrolled formation of carbon–carbon bonds is at the core of the science of organic synthesis. In the context of economies in synthesis,[1] multiple bond-forming transformations (MBFTs)[2] allowing for the sequential creation of two or more C–C bonds in a single chemical operation are particularly valuable. As to the formation of six-membered azacycles, the aza-Diels–Alder (aza-DA) strategy, often involving stepwise nonconcerted processes, counts among the most reliable MBFT-based approaches.[3] Formal aza-DA reactions generally fall into two main categories according to the electronic properties of the reaction partners: normal electron-demand (NED) aza-DA with electron-rich dienes and electron-impoverished imines and inverse electron-demand (IED) aza-DA with electron-deficient 1- or 2-azadienes and electron-rich olefins.[3] It should be noted that only aza-DA cycloadditions with 2-aza-dienes allow for the formation of two C–C bonds. The Povarov reaction, i.e., the IED aza-DA reaction between *N*-aryl imines and electron-rich olefins to give tetrahydroquinolines, is an archetypal example of the reactivity of 2-aza-dienes.[3c,f] The realization of regio- and stereoselective NED Povarov-type reactions with electron-enriched *N*-aryl imines and electron-poor olefins would greatly expand the scope and possible applications of this strategy. However, this complementary reactivity of *N*-aryl imines has remained unstudied.

α-Oxo-ketenes are electrophilic reactive intermediates with a rich chemistry.[4] The microwave-assisted Wolff rearrangement of 2-diazo-1,3-diketones is an extremely efficient and convenient source of α-oxo-ketenes,[5,6] and this technology has recently allowed revisiting their fundamental reactivity. α-Oxo-ketenes normally react with imines as 4π reaction partners in formal IED aza-DA cycloadditions to afford the corresponding oxazinones (Scheme 1, top).[7] It was recently uncovered that their reactions with electron-rich 1-aza-dienes were following an alternative path, involving formal NED aza-DA cycloadditions in which the

Scheme 1. Known and Proposed Aza-DA Cycloadditions with α-Oxo-ketenes[a]



[a]IED = inverse electron-demand; aza-DA = aza-Diels–Alder; NED = normal electron-demand.

C=C bond of the α-oxoketene is this time the 2π reaction partner, leading to stereodefined δ-lactam products with successive C–N and C–C bond-forming events (Scheme 1,

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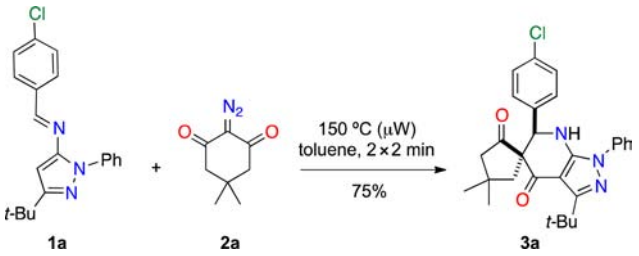
right).[8] A similar reactivity was also observed in the 1,3-dipolar cycloadditions of electron-rich hydrazones with α-oxoketenes.[9] Lately, α-oxoketenes were found to be valuable electrophilic reaction partners in Friedel–Crafts α-ketoacylations of heteroaromatic compounds.[10] Herein, we report regioselective and diastereoselective NED Povarov-type reactions with α-oxoketene dienophiles for the preparation of stereodefined spiro compounds (Scheme 1, gray highlight). This idea was based on the mechanistic hypothesis that a catalyst-free domino Wolff rearrangement/Friedel–Crafts α-ketoacylation/intramolecular Mannich sequence would be possible.

Because of its excellent reactivity in Friedel–Crafts α-ketoacylations[10] and the availability of the corresponding 5-amino derivatives,[11] the pyrazolyl group was selected as the prototypical *N*-aryl moiety to prepare electron-rich *N*-aryl imines amenable to the planned transformation.[12] It can be noted that the first Povarov reactions (IED aza-DA) with aminopyrroles and aminopyrazoles were reported only recently.[13] The present study was initiated with the reaction of the *N*-aryl imine **1a** with the α-oxoketene derived from diazodimedone (**2a**, 1.5 equiv) at 150 °C under microwave irradiation for 6 min. Gratifyingly, the expected spiro hydropyrid-4-one product **3a** resulting from a formal regio- and stereoselective NED Povarov-type reaction was obtained in 65% yield as a single diastereomer. In a modified protocol, the addition of 2.4 equiv of the diazo compound **2a** in two portions afforded the same product **3a** in an increased 75% yield (Scheme 2) together with some dimerization product of the α-oxoketene.[4a,b]

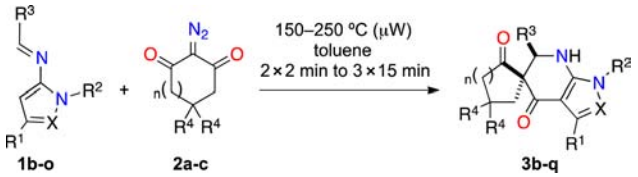
Scheme 2. Regio- and Diastereoselective NED Povarov-Type Reaction



The scope of the reaction was then investigated with several *N*-pyrazolyl imines and a few cyclic 2-diazo-1,3-diketones (Table 1). The reaction was found to be general, and diversely substituted and functionalized NED Povarov-type spiro products **3** could be stereoselectively prepared. Depending on the substrate, reaction temperatures ranging from 150 to 250 °C were required with reaction times varying from 2 × 2 min to 3 × 15 min (see Supporting Information for experimental details). It was found that the pyrazolyl group well tolerated either alkyl or aryl R^1 and R^2 substituents, as well as electron-donating and electron-withdrawing functional groups. In some cases, especially those involving substrates bearing an electron-withdrawing group, minor amounts of the other possible diastereomer were also formed (Table 1, entries 8, 9, and 13).

As a general tendency, more electron-donating substituents on the 2-aza-diene substrate led to higher yield and diastereoselectivity (compare for example Table 1, entries 7, 8, and 9). The reaction appeared more difficult with the α-oxo-ketene derived from the seven-membered diazo compound **2c** (n = 2, R^4 = H), requiring the highest temperature and longest reaction time of

Table 1. Generalization of the Reaction[a]



entry	3; X, R^1, R^2, R^3, R^4, n	dr[b]	yield (%)[c]
1	**3b**; N, *t*-Bu, Ph, 4-Me-C_6H_4, Me, 1	>25:1	81
2	**3c**; N, *t*-Bu, Ph, 4-OMe-C_6H_4, Me, 1	>25:1	70
3	**3d**; N, *t*-Bu, Ph, 3,4-(OCH_2O)-C_6H_3, H, 1	>25:1	79
4	**3e**; N, *t*-Bu, Ph, 4-Me-C_6H_4, H, 1	>25:1	72
5	**3f**; N, *t*-Bu, Ph, 2-OMe-C_6H_4, H, 1	>25:1	51
6	**3g**; N, Me, Ph, 4-OMe-C_6H_4, Me, 1	>25:1	76
7	**3h**; N, *t*-Bu, Me, 4-OMe-C_6H_4, Me, 1	>25:1	80
8	**3i**; N, *t*-Bu, Me, 4-CF_3-C_6H_4, Me, 1	11:1	57
9	**3j**; N, *t*-Bu, Me, 3,5-(CF_3)$_2$-C_6H_4, Me, 1	4:1	36
10	**3k**; N, *t*-Bu, Me, 4-OMe-C_6H_4, H, 2	>25:1	30
11	**3l**; N, Ph, Me, 4-OMe-C_6H_4, Me, 1	>25:1	81
12	**3m**; N, 4-Me-C_6H_4, Me, 4-OMe-C_6H_4, Me, 1	>25:1	73
13	**3n**; N, 4-Cl-C_6H_4, Me, 4-OMe-C_6H_4, Me, 1	17:1	63
14	**3o**; N, Ph, Ph, 4-OMe-C_6H_4, Me, 1	>25:1	41
15	**3p**; N, 4-F-C_6H_4, Ph, 4-OMe-C_6H_4, H, 1	>25:1	31
16	**3q**; CH, CN, *t*-Bu, 4-OMe-C_6H_4, Me, 1	1.4:1	58

[a]Reaction conditions: **1b–o** (0.25 mmol), **2a–c** (0.30–0.90 mmol) added in 1–3 portions, anhydrous toluene (2 mL); see Supporting Information for details. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Based on isolated product after silica gel chromatography.

the study to obtain the desired NED Povarov-type spiro product **3k** in 30% yield (Table 1, entry 10).

The structure of the spiro hydropyrid-4-one **3b** was resolved by X-ray diffraction techniques, which confirmed the chemo-, regio-, and stereochemical outcome of the reaction.[14] Remarkably, the NED Povarov-type reactions described herein allows for the regio- and stereocontrolled formation of two C–C bonds and two contiguous stereogenic carbon atoms, including a challenging "all-carbon" quaternary center.[15] Very interestingly, the reaction could be extended to the pyrrole series in the case of product **3q** (Table 1, entry 16).[16]

The postulated mechanism of the reaction was examined by DFT theoretical calculations using the B3LYP functional with the extended base set 6-311++G** to account for long-range interactions (Scheme 3 and Supporting Information). Our preliminary results[17] indicate that the proposed Friedel–Crafts/Mannich sequence is very plausible, with reasonable transition state energies (activation barrier of 13.8 kcal/mol). In the calculated reaction path, the Friedel–Crafts α-ketoacylation step (**A** → **B** → **C**) occurs through a nucleophilic addition/1,5-proton shift involving the ketone oxygen atom of the α-oxoketene.[18] The intramolecular Mannich step (**C** → **D**) would then ensue as a rare example of concerted asynchronous proton transfer/6-enol exo-endo trig cyclization, which dictates the stereochemical outcome of the reaction (Figure 1). It is believed that with electron-impoverished substrates (e.g., in Table 1, entries 8 and 9) having a less basic nitrogen atom of the imine moiety looser transition states of type TS_{CD} with weaker stabilizing O–H–N interactions are produced, leading to an erosion of the diastereoselectivity.

When the reactions presented in Table 1 were attempted with the five-membered diazo compound **2d**, the pyrazolopyridines

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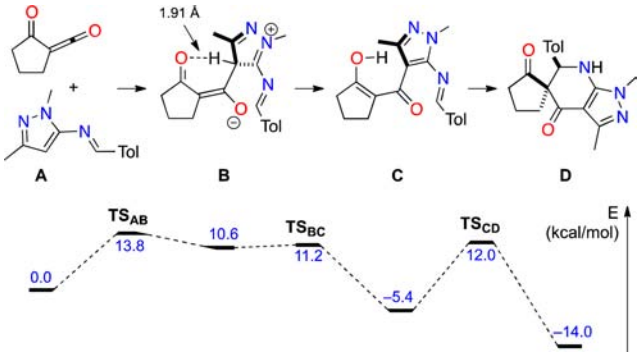
Scheme 3. Theoretical Study of the Proposed Mechanism[a]



[a]Energy profile computed at the B3LYP/6-311++G** level including ZPE correction using the IEFPCM solvation model for toluene.

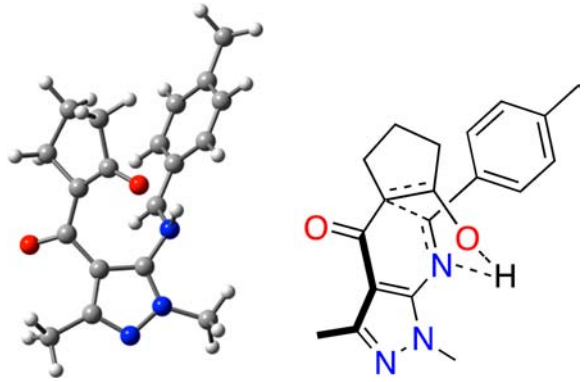
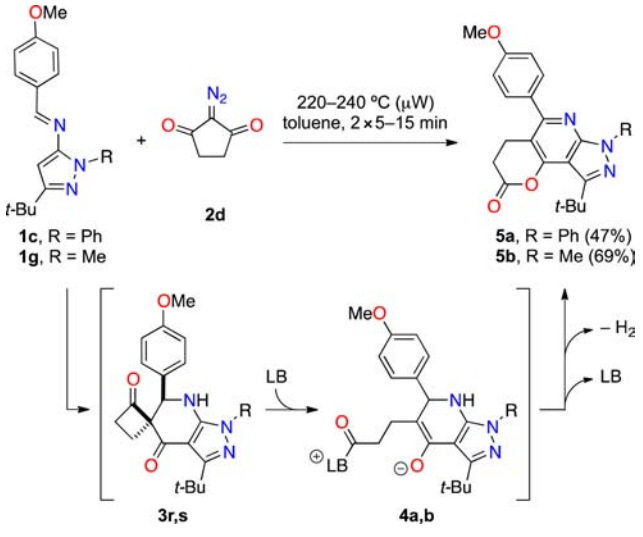


Figure 1. Calculated (left) and schematized (right) transition state TS_{CD}.

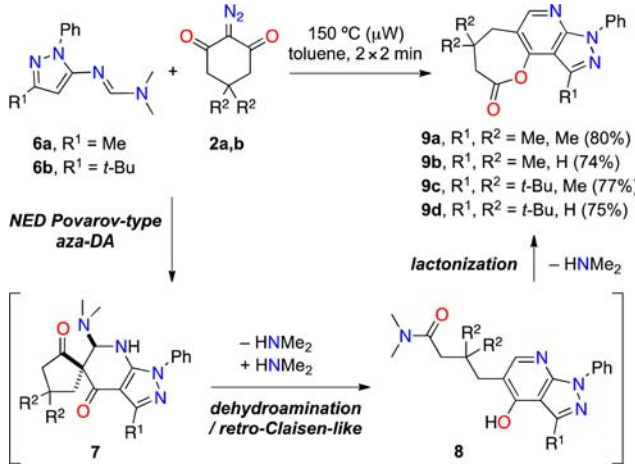
products **5a** and **5b** were obtained instead of the expected spiro cyclobutanone products **3r** and **3s** (Scheme 4). Because of the intrinsic ring strain of cyclobutanones, the formation of products **5a** and **5b** is believed to result from a Lewis base catalyzed ring-rearrangement/oxidation domino sequence via the zwitterionic intermediates **4a** and **4b**, respectively. Although no external Lewis base or oxidant was added to the reaction mixtures, the nucleophilic species responsible for the prolonged domino transformation might be either the starting imines **1** or the intermediates **3** themselves, and oxidation is probably occurring with dissolved oxygen gas.

Scheme 4. Prolonged NED Povarov-Type Aza-DA



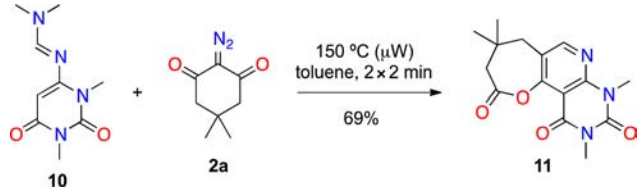
The pyrazolopyridine ring system found in products **5a,b** is a heterocyclic core amenable to applications in medicinal chemistry.[19] It was reasoned that a straightforward access to the related pyrazolopyridine derivatives **9a–d** could rely on the utilization of formimidamides **6a** and **6b** bearing a noninnocent dimethylamino group. This could allow for an original domino sequence initiated by the NED Povarov-type reaction described above to give the intermediate cycloadducts **7**, followed by a dehydroamination/retro-Claisen-like/lactonization cascade (Scheme 5). The *N,N*-dimethyl-*N*′-pyrazolylformimidamides

Scheme 5. Domino Approach to Functionalized Pyrazolopyridine Derivatives



6a and **6b** suitable for the designed MBFT were prepared from the corresponding aminopyrazoles and *N,N*-dimethylformamide dimethyl acetal.[12e] Satisfactorily, their reactions with the diazo compounds **2a** and **2b** afforded the tricyclic products **9a–d**, probably via the anticipated domino sequence. The structure of product **9c** was secured by X-ray diffraction analysis.[14] The scope of the domino reaction could be successfully extended to the formimidamide **10** derived from 6-aminouracil to provide the functionalized pyridopyrimidine **11** (Scheme 6).

Scheme 6. Domino Approach to a Functionalized Pyridopyrimidine



In summary, normal electron-demand Povarov-type cycloadditions proved possible between some electron-rich *N*-aryl imines and cyclic α-oxo-ketenes. The reaction chemo- and regioselectively produced spiro hydropyrazolopyrid-4-ones with good to excellent diastereoselectivities, and is probably occurring via a domino Wolff/Friedel–Crafts/intramolecular Mannich process forming consecutively two carbon–carbon bonds. In a series of divergent reactions, the ring recombination of the Povarov-type products via prolonged domino processes has led

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to fused tricyclic pyrazolopyridine and pyridopyrimidine heterocycles. The elaborate MBFTs described herein (up to 6 steps in the domino process) were built on the functional group density and rich chemistry of α-oxo-ketene reactive intermediates and are expected to open new opportunities for heterocycle and alkaloid synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Details for the mechanistic computational study presented in Scheme 3 and Figure 1, detailed experimental procedures, full characterization data, CIFs for compounds **3b** and **9c**, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605.

(2) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2013**, *19*, 2218.

(3) (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (b) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. *Org. React.* **2005**, *65*, 141. (c) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (d) Girling, P. R.; Kiyoib, T.; Whiting, A. *Org. Biomol. Chem.* **2011**, *9*, 3105. (e) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63. (f) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902.

(4) Reviews on α-oxo-ketenes: (a) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219. (b) Kollenz, G.; Ebner, S. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Danheiser, R., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2006; Vol. *23*, Chapter 9, p 271. (c) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022.

(5) Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415.

(6) Applications: (a) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2011**, *17*, 2048. (b) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2011**, 5061. (c) Castillo, J.-C.; Presset, M.; Abonia, R.; Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2012**, 2338.

(7) Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2009**, *11*, 5706.

(8) Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 4212.

(9) Presset, M.; Mohanan, K.; Hamann, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2011**, *13*, 4124.

(10) Mohanan, K.; Presset, M.; Mailhol, D.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2012**, *18*, 9217.

(11) Anwar, H. F.; Elnagdi, M. H. *Arkivoc* **2009**, No. i, 198.

(12) A few examples of nonregioselective or nonstereoselective aza-DA reactions with *N*-pyrazolyl imines have been documented: (a) Díaz-Ortiz, A.; de la Hoz, A.; Langa, F. *Green Chem.* **2000**, *2*, 165. (b) Mason, H. J.; Wu, X.; Schmitt, R.; Macor, J. E.; Yu, G. *Tetrahedron Lett.* **2001**, *42*, 8931. (c) Muravyova, E. A.; Shishkina, S. V.; Musatov, V. I.; Knyazeva, I. V.; Shishkin, O. V.; Desenko, S. M.; Chebanov, V. A. *Synthesis* **2009**, 1375. (d) Nascimento-Júnior, N. M.; Mendes, T. C. F.; Leal, D. M.; Corrêa, C. N. M.; Sudo, R. T.; Zapata-Sudo, G.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 74. (e) Quiroga, J.; Valencia, A.; Pérez, A.; Gálvez, J.; Abonia, R.; Insuaty, B. *Lett. Org. Chem.* **2013**, *10*, 337.

(13) Brioche, J.; Courant, T.; Alcarez, L.; Stocks, M.; Furber, M.; Zhu, J.; Masson, G. *Adv. Synth. Catal.* **2014**, *356*, 1719.

(14) The CIF for **3b** and **9c** are available as Supporting Information.

(15) (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (c) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (d) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (e) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593.

(16) The reactions of **2a** with (*E*)-4-methoxy-*N*-(4-methoxybenzylidene)aniline or 3-(*tert*-butyl)-*N*-cyclopentylidene-1-phenyl-1*H*-pyrazol-5-amine were found to be unproductive.

(17) A comprehensive theoretical study on the cycloaddition reactions of α-oxo-ketenes with imines and aza-dienes is ongoing and will be reported in due course.

(18) Mono- and bimolecular paths involving the ketene oxygen atom of the α-oxo-ketene were also examined for the proton transfer step (1,3-proton shift) and were found less favorable.

(19) Pyrazolopyridines form a class of nonbenzodiazepine anxiolytic drugs acting as positive allosteric modulators of the $GABA_A$ receptor at the barbiturate binding site; known examples include Cartazolate, Etazolate, ICI-190,622, and Tracazolate. See: Shi, D.; Padgett, W. L.; Hutchinson, K. D.; Moore, S. P.; Daly, J. W. *Drug Dev. Res.* **1997**, *42*, 41.